

APO-SUMATRIPTAN

1. APO-SUMATRIPTAN (50mg & 100mg film coated tablets)

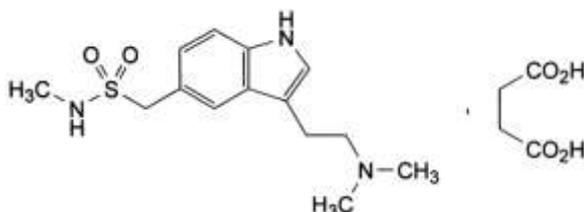
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sumatriptan 50mg or 100mg (as succinate)

Chemical Structure:

Sumatriptan Succinate is chemically described as [3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulphonamide hydrogen butanedioate.

Its empirical formula is C₁₈H₂₇N₃O₆S and its structural formula is:



Sumatriptan succinate is White or almost white powder with a molecular weight of 413.5. Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

Excipient(s) of known effect

Apo-Sumatriptan does not contain gluten.

Apo-Sumatriptan contains lactose.

If you have been told by your doctor that you have intolerance to some sugars contact your doctor before taking this medicinal product.

Contains 135 mg of lactose monohydrate per 50 mg and 85 mg of lactose monohydrate per 100 mg.

This should be taken into account in patients with diabetes mellitus.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Apo-Sumatriptan 50 mg film-coated tablet: are peach coloured, capsule shaped, biconvex film coated tablet engraved "BL" on one side and plain on the other side. Each tablet typically weighs 153mg.

Apo-Sumatriptan 100 mg film-coated tablet: are white, capsule shaped, biconvex film coated tablet engraved "BL" on one side and plain on the other side. Each tablet typically weighs 306mg.

Film coated tablet cannot be halved.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Apo-Sumatriptan Tablets are indicated for the acute relief of migraine attacks with or without aura.

4.2 Dose and method of administration

Apo-Sumatriptan Tablets should not be used prophylactically.

The recommended dose of sumatriptan should not be exceeded.

It is advisable that Apo-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.

Dose

The recommended adult dose of oral Apo-Sumatriptan is a 50mg tablet. Some patients may require 100mg.

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

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

Children and Adolescents (under 18 years of age)

The safety and effectiveness of sumatriptan in children has not yet been established.

Elderly (over 65)

Experience of the use of sumatriptan in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population, but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

Administration in hepatic impairment (Martindale)

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

Maximum Tolerated Daily Dose

Not more than 300mg should be taken in any 24-hour period.

Method of administration

The tablets are to be administered orally.

The tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to any component of the preparation.

Sumatriptan should not be given to patients who have had a myocardial infarction or have ischaemic heart disease (IHD), Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.

Sumatriptan should not be administered to patients with a history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

The use of sumatriptan in patients with uncontrolled hypertension is contraindicated.

Sumatriptan should not be administered to patients with severe hepatic impairment.

The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see Interaction with other medicines and other forms of interaction).

Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated. Sumatriptan must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Apo-Sumatriptan Tablets 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.

Before treating with sumatriptan, care should be taken to exclude potentially serious neurological conditions (e.g. CVA, TIA) if the patient presents with atypical symptoms or if they have not received an appropriate diagnosis for sumatriptan use. Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see Undesirable 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 a 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 postmarketing reports describing patients with serotonin syndrome (including altered mental status, autonomic 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 with other medicines and other forms of interaction).

The concomitant administration of any triptan/5-HT₁ agonist 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 medicine, eg. impaired hepatic (Child Pugh grade A or B; see Pharmacokinetics – Special Patient Populations) or renal function (see Pharmacokinetics).

Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.

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 the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been reported with use of serotonergic agents such as SSRIs or triptans.

Chronic use can result in a rebound headache.

Do not use if you have an irregular heartbeat.

Do not use if you are allergic to sulfonamides.

Do not use with other migraine medications except on doctor's advice.

Do not use if you are pregnant except on doctor's advice.

4.5 Interactions with other medicines and other forms of interactions

Pharmacokinetics 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, 24 hours should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 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 Special Warnings and Precautions for use).

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 SSRIs and sumatriptan.

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

4.6 Fertility, pregnancy and lactation

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 registries have documented the pregnancy outcomes in over 1,000 women exposed to sumatriptan. Although there is insufficient information to draw definitive 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 embryoletality at doses which were sufficiently high to produce maternal toxicity.

Lactation

It has been demonstrated that following subcutaneous administration sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment.

4.7 Effects on ability to drive and use machines

Likely to produce minor or moderate adverse effects on the ability to drive or use machinery. Drowsiness may occur as a result of migraine or its treatment with sumatriptan.

Caution is recommended in patients performing skilled tasks, eg. driving or operating machinery.

4.8 Undesirable 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.

Post-Marketing Data Clinical Trial Data

Nervous System Disorders

Common: 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

The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:

Common: Sensations of heaviness.

General Disorders and Administration Site Conditions

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:

Common: Pain, sensations of heat or cold, pressure or tightness.

The following symptoms are mostly mild to moderate in intensity and transient:

Common: Feelings of weakness, fatigue.

Investigations

Very rare: Minor disturbances in liver function tests have occasionally been observed.

Immune System Disorders

Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to 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. Tremor, dystonia, nystagmus, scotoma.

Eye disorders

Very rare: Flickering, diplopia, reduced vision. Loss of vision (usually transient). 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, angina, myocardial infarction (see Contraindications, Special Warnings and Precautions for use).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Very rare: Ischaemic colitis.

Post-marketing Experience

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 SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see Special Warnings and Precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Doses in excess of 400mg orally were not associated with side effects other than those mentioned. If overdosage 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

ATC code: N02CC01 Analgesic, antimigraine preparation, selective serotonin (5HT1)

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5HT1D) receptor agonist with no effect at other 5HT receptor (5HT2 -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 and dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. 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 10-15 minutes following a 6mg subcutaneous injection, and around 30 minutes following a 100mg oral dose.

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

5.2 Pharmacokinetic properties

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

Absorption

After oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After a 100mg dose the mean maximum plasma concentration is 54ng/mL.

Mean absolute oral bioavailability is 14% partly due to pre-systemic metabolism and partly due to incomplete absorption.

Distribution

Plasma protein binding is low (14-21%); the mean total volume of distribution is 170 litres.

Metabolism

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.

Elimination

The elimination half-life is approximately 2 hours. The mean total plasma clearance is approximately 1160mL/min and the mean renal plasma clearance is approximately 260mL/min.

Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.

Special patient populations

Hepatic impairment

Following oral administration, pre-systemic clearance is reduced in patients with hepatic impairment resulting in increased plasma levels of sumatriptan (see Special Warnings and Precautions for use).

5.3 Preclinical safety data

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

In a rat fertility study oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man after a 100mg 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apo-Sumatriptan film coated tablets contain the following excipients:

- Lactose Monohydrate
- Microcrystalline Cellulose
- Pregelatinised starch
- Croscarmellose sodium
- Magnesium Stearate
- Purified Water
- Hypromellose
- Titanium Dioxide
- Purified Talc
- Macrogol 6000

The 50mg strength contains additionally colourant:

- Ferric oxide red
- Ferric oxide yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25°C
Protect from light.

6.5 Nature and contents of container

Apo-Sumatriptan 50mg tablets are available in blister packs of 2, 4, 6, 12, 100, 102 and 500 tablets.

Apo-Sumatriptan 100 mg tablets are available in blister packs of 6, 12, 100 and 102 tablets

Not all pack types or pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

Restricted Medicine for Apo-Sumatriptan 50mg packs of two tablets only.

8. SPONSOR

Apotex NZ Ltd
 32 Hillside Road
 Glenfield
 Private Bag 102-995
 North Shore Mail Centre
 Auckland
 Telephone: (09) 444 2073
 Fax: (09) 444 2951

9. DATE OF FIRST APPROVAL

02 April 2015

10. DATE OF REVISION OF THE TEXT

22 November 2016

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new guideline for data sheet.
4.8	Additional information based on new data sheet format.
4.9	Additional information based on new data sheet format.
6.5	Packaging descriptive information added to provide information required in new data sheet format "Not all pack types pack sizes may be marketed" statement added to provide all information required in new data sheet format
6.6	New section and information required in new data sheet format
8	Change in sponsor
9	New section and information required in new data sheet format
Summary Table of Changes	New section and information required in new data sheet format