

MyGran

Sumatriptan (as succinate) 50 mg tablets

Presentation

MyGran is a white to off-white, round, biconvex tablet, embossed with 'SA' over '50' on one side and '>' 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.

Sumatriptan relieves headache and other symptoms of migraine including nausea, and sensitivity to light and sound. It remains effective in treating menstrual migraine, i.e. migraine without aura that occurs between 3 days prior to and up to 5 days post onset of menstruation.

Clinical response for relief of migraine headache begins around 30 minutes following a 50 mg oral dose. Sumatriptan should be taken as soon as possible after the onset of a migraine headache.

Pharmacokinetics

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

Absorption

After oral administration, sumatriptan is rapidly absorbed with 70% of maximum concentration occurring at 45 minutes. After a 50 mg dose, mean maximum plasma concentration is 32 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.

Distribution

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

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

Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The elimination phase half-life is approximately 2 hours, although there is an indication of a longer terminal phase. 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.

Elderly and special patient groups

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.

Indications

MyGran is indicated for acute relief of migraine attacks, with or without aura. It relieves migraine headache and the associated symptoms of nausea and sensitivity to light and sound.

MyGran should only be used where there is a clear diagnosis of migraine.

Dosage and Administration

MyGran should not be used prophylactically. Administration during a migraine aura, prior to other symptoms occurring, may not prevent the development of a headache.

Adults (18 to 65 years of age)

The recommended dose of sumatriptan is a single 50 mg tablet. The tablet should be swallowed whole with water, without regard to meals. It is recommended to start the treatment at the first sign of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. However, it is effective at whatever stage of the attack it is taken.

If there is a response to the first tablet but the symptoms recur, a second tablet may be taken. However, this must be at least 2 hours after the first tablet. No more than two 50 mg tablets (total dose 100 mg) may be taken in any 24-hour period or to treat the same attack.

If there is no response to the first tablet, a second tablet should not be taken for the same attack. Simple analgesics can be used to relieve the headache. Sumatriptan may be taken for subsequent attacks.

Children and adolescents (under 18 years of age)

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 children or adolescents under the age of 18.

Elderly (over 65 years of age)

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

MyGran must not be used prophylactically.

MyGran is contraindicated in patients who have:

- hypersensitivity to sulphonamides or to any component of the product (see **Further Information**)
- a history of myocardial infarction
- ischaemic heart disease (IHD), symptoms or signs consistent with IHD
- Prinzmetal's angina or coronary vasospasm
- cardiac arrhythmias
- peripheral vascular disease
- a history of previous cerebrovascular accident (stroke) or transient ischaemic attack (mini-stroke)
- uncontrolled hypertension
- hepatic or renal impairment
- history of seizures or other risk factors that lower the seizure threshold.

Concurrent therapy of MyGran with the following medications is contraindicated:

- within 24 hours of treatment with an ergotamine or ergot-type medication such as dihydroergotamine or methysergide (see **Interactions**)
- monoamine oxidase inhibitors (MAOIs); and within 2 weeks of discontinuing MAOI therapy
- any 5HT₁ receptor agonist (triptans).

MyGran is not to be used to treat the following rare variants of migraine:

- hemiplegic migraine - migraine with aura including unilateral motor weakness
- basilar migraine - migraine with aura symptoms originating from the brain stem and/or both hemispheres such as double vision, difficulty in articulating words, clumsy and uncoordinated movements, tinnitus, reduced level of consciousness

- ophthalmoplegic migraine - migraine headache with involvement of one or more ocular cranial nerves resulting in weakness of the muscles controlling eye movement.

Warnings and Precautions

MyGran should only be used where a clear diagnosis of migraine has been made by a doctor. For pharmacy supply, patients should have a stable, well-established pattern of migraine.

MyGran should not be taken concomitantly with other migraine therapies containing any triptan, ergotamine or ergot-type medications.

If the patient does not respond to the first dose, a second dose should not be taken. The headache may be treated with simple analgesics. Also, the diagnosis of migraine should be reviewed again by a doctor.

The recommended doses of MyGran should not be exceeded.

Migraineurs should seek advice from their doctor if:

- typical headaches persist for longer than 24 hours
- pattern of symptoms has changed, or whose attacks have become more frequent, more persistent or more severe, or who do not recover completely between attacks
- atypical symptoms occur, which include, but are not limited to, unilateral motor weakness, double vision, clumsy and uncoordinated movements, tinnitus, reduced level of consciousness, seizure-like movements, or recent onset of rash with headache
- migraine symptoms appear for the first time after age 50, as there may be a more serious underlying cause
- experience four or more migraine attacks per month, as ongoing management would be required.

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

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**). Typically, such symptoms develop within 30 minutes of treatment and last for less than 2 hours. Where such symptoms are thought to indicate IHD, medical evaluation should be obtained immediately and no further doses of sumatriptan should be taken until considered appropriate by a doctor.

Sumatriptan should not be given to migraineurs in whom risk factors indicate a possibility of unrecognised coronary artery disease (CAD). Risk factors for CAD include hypertension, hypercholesterolaemia, smoking, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age. Anyone who has three or more of these risk factors is not suitable for pharmacy supply of sumatriptan. These factors may not identify everyone who has cardiac disease and, in very rare cases, serious cardiac events have occurred without underlying cardiovascular disease. Thus, 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, 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 IHD, 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.

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.

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.

Hypersensitivity

Patients with known hypersensitivity to sulfonamides may exhibit an allergic reaction following administration of sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Although evidence of cross sensitivity is limited, treatment with sumatriptan is contraindicated in these patients (see Contraindications).

Lactose and/or galactose intolerance

MyGran contains lactose. Patients with lactose intolerance, rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Renal or hepatic impairment

Sumatriptan should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism and/or excretion of the drug, such as hepatic or renal impairment. Studies have shown a decrease in 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.

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.

Selective serotonin reuptake inhibitors (SSRIs)

There have been rare post-marketing reports describing patients with transient weakness, hyper-reflexia and incoordination following use of a SSRI with sumatriptan. If concomitant use is considered to be appropriate, migraineurs should be warned to see their doctor if they develop weakness and incoordination following treatment.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (*Hypericum perforatum*).

Oral contraceptives

Female migraineurs who are taking the combined oral contraceptive have an increased risk of stroke. Seek advice from doctor for recent migraine attacks (started within the last 3 months), worsening migraine symptoms or migraines with aura.

Overuse of sumatriptan

As with other acute migraine treatments, chronic daily headache/exacerbation of headache have been reported with overuse of sumatriptan and this may necessitate a drug withdrawal.

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.

In rabbits, embryoletality was seen without marked teratogenic defects. The relevance for humans of these findings is unknown.

Use in pregnancy (Category B3)

Sumatriptan should not be used in pregnancy unless the expected benefit to the mother is greater than any possible risk to the foetus.

Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. While there is insufficient data to draw definite conclusions, the findings do not suggest an increased risk of congenital defects amongst pregnant women exposed to sumatriptan compared with the general population. Experience with the use of sumatriptan in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and post-natal development. Reproduction studies in rats have not revealed any clear evidence of impaired fertility or of impaired post-natal pup development. However, when administered to pregnant rabbits throughout the period of organogenesis, sumatriptan has caused embryoletality at doses that were sufficiently high to produce maternal toxicity (see **Preclinical safety data**). Term foetuses from Dutch Stride rabbits treated during the period of organogenesis with oral sumatriptan exhibited an increased incidence of cervico-thoracic 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

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$), <

1/10), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) and very rare ($< 1/10,000$) including isolated reports.

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

Common: Dizziness, drowsiness, sensory disturbances including paraesthesia and hypoaesthesia.

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), nystagmus, scotoma, tremor, dystonia.

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, myocardial infarction (see **Contraindications, Warnings and Precautions**).

Vascular disorders

Common: Transient increases in blood pressure (arising soon after treatment), flushing.

Very rare: Hypotension, Raynaud's phenomenon.

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.

Very rare: Ischaemic colitis.

Musculoskeletal and connective tissue disorders

Common: Sensations of heaviness, which are usually transient and 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, which are usually transient and may be intense and can affect any part of the body including the chest and throat.

Common: Feelings of weakness or fatigue, which are mostly mild to moderate in intensity and transient.

Laboratory results

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

Interactions

Sumatriptan has the potential to interact with MAOIs, ergotamine and derivatives of ergotamine. The increased risk of coronary vasospasm is a theoretical possibility and therefore concomitant administration with MAOIs and ergotamine is contraindicated (see **Contraindications**).

Pharmacodynamic

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 (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.

There is a risk of pharmacodynamic interaction between sumatriptan and tricyclic antidepressants.

Pharmacokinetic

An interaction may occur between sumatriptan and MAOIs, and concomitant administration is contraindicated (see **Contraindications**). Also, sumatriptan should not be given within 2 weeks of discontinuing MAOI therapy.

Rarely, an interaction may occur between sumatriptan and SSRI. There have been rare post-marketing reports describing patients with weakness, hyper reflexia and incoordination following the use of an SSRI (see **Warnings and Precautions**). If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Interactions with other drugs

Although there is no clear evidence, it is possible that an interaction may occur during concurrent use of triptans and the herbal remedy St John's wort (*Hypericum perforatum*), which may result in an increase in side effects.

Studies in healthy subjects show that sumatriptan does not interact with propranolol, flunarizine, pizotifen or alcohol.

Overdosage

In the event of an overdose, medical advice should be sought immediately.

There have been some reports of overdosage with sumatriptan. Doses in excess of 400 mg orally were not associated with side effects other than those mentioned.

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

48 months

Storage

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

Medicine Classification

Restricted Medicine

Package Quantities

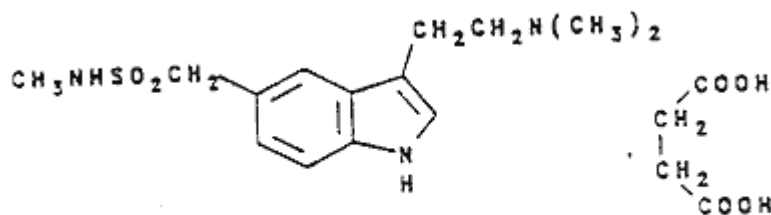
Blister pack of 2 tablets

Further Information

MyGran contains 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 C₁₄H₂₁N₃O₂S 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:



C₁₄H₂₁N₃O₂S·C₄H₆O₄ Molecular weight: 413.5 g/mol CAS: 103628-46-2

MyGran tablets contain microcrystalline cellulose, croscarmellose sodium, magnesium stearate and anhydrous lactose. The tablets are gluten free.

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Date of Preparation

14th July 2011