

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

SUMATRAN 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg sumatriptan (as sumatriptan succinate).

Excipient with known effect:

Each tablet contains 116.20 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White/off-white, biconvex, oblong tablet with a break-line on both sides.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

General recommendations with regard to use and administration:

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

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.

Posology

The following recommended dosages of Sumatriptan should not be exceeded.

Adults

The recommended dosage for adults is 50 mg sumatriptan. Some patients may require 100 mg sumatriptan.

Although the recommended oral dose of sumatriptan is 50 mg, it must be taken into account that the severity of migraine attacks varies both within and between patients. Doses of 25 mg-100 mg have shown to be more effective than placebo in clinical trials but 25 mg is statistically significantly less effective than 50 mg and 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. In these cases the attack can be treated with paracetamol, acetylsalicylic acid, or non-steroidal anti-inflammatory drugs. Sumatriptan tablets 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 there is a minimum interval of 2 hours between the two doses. No more than 300 mg should be taken in any 24- hour period.

Paediatric population

The efficacy and safety of sumatriptan tablets in children aged less than 10 years have not been established. No clinical data are available in this age group.

The efficacy and safety of sumatriptan tablets in children 10 to 17 years of age have not been demonstrated in the clinical trials performed in this age group. Therefore, the use of sumatriptan tablets in children 10 to 17 years of age is not recommended (see section 5.1).

Older people (over 65 years of age)

Experience of the use of sumatriptan tablets 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.

Patients with hepatic insufficiency

In patients with mild to moderate hepatic insufficiency low doses of 25-50 mg sumatriptan should be considered.

Method of administration

The tablets must be taken with water. The sumatriptan substance has a bitter taste. The bitter taste is masked with the aid of a grapefruit flavour.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- A history of myocardial infarction, ischaemic heart disease or coronary vasospasm (Prinzmetal's angina)
- Peripheral vascular disease
- Symptoms or signs consistent with ischaemic heart disease
- A history of stroke (cerebrovascular accident (CVA)) or transient ischaemic attack (TIA)
- Severe hepatic impairment
- Moderate to severe hypertension, mild uncontrolled hypertension
- Concomitant administration of preparations containing ergotamine or ergotamine derivatives (including methysergide) or any triptan/5-hydroxytryptamine 1 (5-HT₁) receptor agonist (see section 4.5)
- Concomitant use of monoamine oxidase inhibitors and the use of sumatriptan within 2 weeks after discontinuation of therapy with monoamine oxidase inhibitors

4.4 Special warnings and precautions for use

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

Sumatriptan is not indicated for use in the management of basilar, hemiplegic 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. CVA, TIA).

Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat (see section 4.8). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan should be given and an appropriate evaluation should be carried out.

Sumatriptan should be given with caution in patients with mild controlled hypertension, since transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients (see section 4.3).

Sumatriptan should not be given to patients with risk factors for ischaemic heart disease, including those patients who are heavy smokers or users of nicotine substitution therapies, without prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 years of age with these risk

factors. These evaluations however, 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 (see section 4.8).

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 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 section 4.5).

Sumatriptan should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism, or excretion of the drug, e.g. impaired hepatic or renal function.

Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold, as seizures have been reported in association with sumatriptan (see section 4.8).

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction after use of sumatriptan. The reactions can vary from cutaneous hypersensitivity to anaphylaxis. Evidence of cross sensitivity is limited, however, caution should be exercised before using sumatriptan in these patients.

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

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

The recommended dosage should not be exceeded.

Patients with rare hereditary conditions such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicine as it contains lactose.

4.5 Interaction with other medicinal products and other forms of interaction

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

There are limited data on an interaction with preparations containing ergotamine or another triptan/5-HT₁ receptor agonist. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated (see section 4.3).

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations or another triptan/5-HT₁ receptor agonist is not known. This will also depend on the doses and type of products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine containing preparations or another triptan/5-HT₁ receptor agonist before administering sumatriptan. Conversely it is advised to wait at least 6 hours following use of sumatriptan before administering an ergotamine containing product and at least 24 hours before administering another triptan/5-HT₁ receptor agonist.

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see section 4.3).

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 section 4.4).

There may be a risk of serotonergic syndrome also if sumatriptan is used concomitantly with lithium.

4.6 Fertility, pregnancy and lactation

Pregnancy

Post-marketing data on the use of sumatriptan during the first trimester of pregnancy in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not point to an increased risk of congenital defects. 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 postnatal development. However, embryo-foetal viability might be affected in the rabbit (see section 5.3). Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding

It has been demonstrated that following subcutaneous administration sumatriptan is secreted into breast milk. Infant exposure can be minimised by avoiding breast-feeding for 12 hours after treatment, during which time any breast milk expressed should be discarded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Drowsiness, dizziness and weakness may occur as a result of migraine or its treatment with sumatriptan. This may influence the ability to drive and to operate machinery.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $<1/10$),

Uncommon ($\geq 1/1,000$ to $<1/100$),

Rare ($\geq 1/10,000$ to $<1/1,000$),

Very rare ($<1/10,000$), not known (cannot be estimated from the available data).

Some of the symptoms reported as undesirable effects may be associated symptoms of migraine.

Immune system disorders

Not known: Hypersensitivity reactions ranging from cutaneous hypersensitivity (such as urticaria) to anaphylaxis.

Psychiatric disorders

Not known: Anxiety.

Nervous system disorders

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

Not known: 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

Not known: Flickering, diplopia, reduced vision. Loss of vision including reports of permanent defects. However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders

Not known: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary

artery vasospasm, angina, myocardial infarction (see sections 4.3 and 4.4).

Vascular disorders

Common: Transient increases in blood pressure arising soon after treatment, flushing.
Not known: Hypotension, Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea.

Gastrointestinal disorders

Common: Nausea and vomiting occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition.
Not known: Ischaemic colitis, diarrhoea.

Skin and subcutaneous tissue disorders

Not known: Hyperhidrosis.

Musculoskeletal and connective tissue disorders

Common: Sensations of heaviness (usually transient and may be intense and can affect any part of the body including the chest and throat), myalgia.
Not known: Neck stiffness, arthralgia.

General disorders and administration site conditions

Common: Pain, sensations of heat or cold, pressure or tightness (these events are usually transient and may be intense and can affect any part of the body including the chest and throat); feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).
Uncommon: Somnolence

Investigations

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

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and Signs

Doses in excess of 400 mg orally and 16 mg subcutaneously were not associated with side effects other than those mentioned. Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects.

Treatment

If overdosage occurs, the patient should be monitored for at least 10 hours and standard supportive treatment applied as required. It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, selective serotonin (5HT₁) agonists
ATC code: N02CC01

Mechanism of action

Sumatriptan is a specific and selective 5-hydroxytryptamine-1d receptor agonist, and has not demonstrated activity on the other 5HT (5HT2-5HT7) receptors.

Pharmacodynamic effects

The vascular 5HT_{1d} receptor is found predominantly in the cranial blood vessels and has a vasoconstrictor effect. In experimental animals, it has been shown that sumatriptan causes vasoconstriction of the arterioles and the arteriovenous anastomata of the carotid vascular bed. This vascular bed provides the blood supply to the extracranial and intracranial tissues, such as the meninges. It has been proposed that dilatation of these arterial vessels, and the formation of oedema here, is the underlying cause of a migraine attack in humans. There is also evidence from animal experiments to suggest that sumatriptan inhibits the activity of the trigeminal nerve. Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) might contribute to the antimigraine effect of sumatriptan in humans.

Clinical efficacy

A clinical response occurs approximately 30 minutes after oral administration of a dose of 100 mg.

Sumatriptan is effective for the acute treatment of migraine attacks that occur during menstruation in women, i.e. in the period from 3 days before to 5 days after the beginning of menstruation.

Paediatric population

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in approximately 800 children and adolescent migraineurs aged 10-17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 10-17 years was similar to that reported from studies in the adult population.

5.2 Pharmacokinetic properties

Absorption

Following oral administration sumatriptan is rapidly absorbed, the maximum concentration being reached after approx. 45 minutes. After oral administration of 100 mg the peak plasma concentration is on average 54 ng/ml. Absolute bioavailability after oral administration is on average 14%. This is partly due to presystemic metabolism and partly to incomplete absorption. In patients with hepatic insufficiency, presystemic clearance after oral administration is reduced, resulting in an increase in the plasma levels of sumatriptan.

Distribution

Protein binding is low (14-21%) and the mean volume of distribution is 170 litres.

Biotransformation and elimination

The elimination half-life is approximately 2 hours. Mean total clearance is 1160 ml/minute and mean renal clearance is approximately 260 ml/minute. Nonrenal clearance is approximately 80% of total clearance, suggesting that sumatriptan is primarily cleared through oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan, is excreted in the urine as the acid or as the glucuronide conjugate. This metabolite has no known 5HT₁ or 5HT₂ activity. Minor metabolites have not been identified.

The pharmacokinetics of the oral administration of sumatriptan does not appear to be influenced by a migraine attack.

Older people

The kinetics in older people has not been sufficiently studied to permit a statement on possible differences in the kinetics between older and young volunteers.

5.3 Preclinical safety data

In a fertility study in the rat, a reduction in the success of insemination was seen on exposure to concentrations higher than the maximum exposure in humans. In rabbits embryoletality was observed, without marked teratogenic effects.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonium methacrylate copolymer type A
carmellose sodium (E466)
microcrystalline cellulose (E450)
croscarmellose sodium (E468)
lactose monohydrate
magnesium stearate (E470b)
flavouring (grapefruit)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sumatriptan tablets are available in Aluminium/aluminium blister strips in a cardboard carton.

2, 3, 4, 6, 12, 18, 19, 20, 24, 30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/81/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 January 2006
Date of last renewal: 1 December 2009

10 DATE OF REVISION OF THE TEXT

Health Products Regulatory Authority

September 2016