

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0688/010/002

Case No: 2024535

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Chanelle Medical

Loughrea, Co. Galway, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sumatriptan 100 mg film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/09/2008** until **11/09/2013**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets, containing Sumatriptan 100 mg base, as sumatriptan succinate

Also contains lactose, for a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off white oblong shaped, film-coated tablets with a score line on one side and embossed with 100 on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the acute relief of severe disabling migraine attacks, (with or without aura).

4.2 Posology and method of administration

Sumatriptan is indicated for the acute intermittent treatment of migraine. Sumatriptan Tablets should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine and should not be given concomitantly with other acute migraine therapies. If a patient fails to respond to a single dose of sumatriptan there are no reasons, either on theoretical grounds or from limited clinical experience, to withhold products containing aspirin or non-steroidal anti-inflammatory drugs for further treatment of the attack.

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.

Adults only:

The recommended adult dose of oral Sumatriptan is a single 50 mg tablet. 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 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 not more than 300 mg is taken in any 24 hour period. An interval of two hours should generally be allowed to elapse between doses.

The tablets should be swallowed whole with water.

Children (under 18 years of age):

The safety and effectiveness of Sumatriptan Tablets 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.

Patients with Hepatic Impairment:

Impairment of hepatic function gives rise to an 80% increase in plasma sumatriptan levels after an oral dose of 100mg. The drug should therefore be used with extreme caution and at reduced dosage in these patients.

Patients with Renal Impairment:

There is no information on the effect of renal impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

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

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

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

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see section 4.5).

Concurrent administration of monoamine oxidase inhibitors (MAOIs) or use within two weeks of discontinuation of MAOI therapy is contraindicated.

Until further data are available the use of sumatriptan is contraindicated in patients receiving concurrent treatment with certain antidepressants e.g. selective 5-HT reuptake inhibitors (see section 4.5) and lithium.

Sumatriptan tablets should not be given to diabetic patients.

4.4 Special warnings and precautions for use

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.

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.

There have been a number of reports of CVA (stroke, paresis), where a temporal association with sumatriptan intake was seen. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. CVA, TIA).

Sumatriptan should not be used in patients with underlying cardiac disorders or in patients who, although asymptomatic, have significant risk factors predisposing to coronary artery disease. Therefore a careful history to exclude pre-existing cardiac disease should be taken before sumatriptan is prescribed. Evaluations may not identify every patient who has cardiac diseases and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease and in the absence of known risk factors.

Patients in whom undiagnosed coronary artery disease is a possibility on the basis of age or the presence of other risk factors, such as family history of coronary artery disease, tobacco smoking, diabetes, hypercholesterolaemia, should receive the product only with great caution and if the benefit of treatment is judged to outweigh the possible risk. Use of sumatriptan should be carefully considered in patients who may be at risk of thrombotic episodes. There have been rare reports of patients on hormone replacement therapy who have had cardiac ischaemic events.

Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat and arms. These symptoms may mimic angina pectoris but, in patients in whom cardiac investigations have been performed, they have only rarely been found to have been the result of coronary vasospasm. Although rare, the vasospasm may result in arrhythmia including ventricular fibrillation/ischaemia or myocardial infarction. If the patient experiences symptoms which are severe or persistent or are consistent with angina, further doses should not be taken until appropriate investigations have been carried out to check for the possibility of ischaemic changes.

There have been a number of fatalities from ventricular fibrillation and myocardial infarction.

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.

Sumatriptan should be administered with caution to patients with conditions, which 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

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 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 SSRI/SNRI is clinically warranted appropriate observation of the patient is advised (see interactions). The concomitant administration of any triptan/5-HT₁ agonist with sumatriptan is not recommended.

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.

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis.

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

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

The recommended dose of sumatriptan should not be exceeded.

4.5 Interaction with other medicinal products and other forms of interaction

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

There are limited data on an interaction with ergotamine containing preparations. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated.

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations is not known. This will also depend on the doses and type of ergotamine containing products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering sumatriptan. Conversely, it is advised to wait at least six hours following use of sumatriptan before administering an ergotamine containing product (see section 4.3).

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see section 4.3). There is a risk of CNS toxicity when both MAOI's and SSRI's are given with Sumatriptan Tablets; hence concomitant use is contraindicated (see section 4.3).

There have been rare-postmarketing 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 Warnings and Precautions).

4.6 Pregnancy and lactation

Pregnancy:

The safety of Sumatriptan Tablets for use in human pregnancy has not been established. Administration of Sumatriptan Tablets should only be considered if the expected benefit to the mother outweighs any possible risk of 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 general population.

Lactation:

It has been demonstrated that following subcutaneous administration sumatriptan is excreted in 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

No studies on the effects on the ability to drive and use machines has been performed. However, drowsiness may occur as a result of migraine or its treatment with Sumatriptan Tablets. Caution is recommended in patients performing skilled tasks, e.g. 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.

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.

Post-Marketing Data:

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 Section 4.3 Contraindications, Section 4.4 Special warnings and precautions).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Very rare: Ischaemic colitis.

4.9 Overdose

There have been some reports of overdose with sumatriptan.

Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Doses up to 16 mg subcutaneously and up to 400 mg orally were not associated with side effects other than those mentioned. There is no experience of doses greater than these.

If overdose 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin 5HT₁ agonists.

ATC code: N02C C01.

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5HT_{1d}) receptor agonist with no effect at other 5HT receptor (5HT₂-5HT₇) subtypes. The vascular 5HT_{1d} receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals sumatriptan selectively constricts the carotid arterial circulation, 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, evidence from animal studies suggests that sumatriptan inhibits trigeminal nerve activity.

Both these actions (cranial vasoconstriction and inhibition of trigeminal nerve activity) may contribute to the anti-migraine action of sumatriptan in humans.

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

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

5.2 Pharmacokinetic properties

Absorption: Rapid. However bioavailability is low (approximately 14% of a dose), primarily because of presystemic hepatic metabolism and, to a lesser extent, because of incomplete absorption. The rate and extent of absorption are not affected to a clinically significant extent by administration with food or by the gastric stasis that may accompany migraine headaches.

Bioavailability is increased by 80% in patients with hepatic impairment.

Distribution: Sumatriptan is rapidly and extensively distributed to tissues, but passage across the blood-brain barrier is limited.

Protein binding: In plasma - low (14 to 21%).

Biotransformation: Hepatic and extensive; approximately 80% of a dose is metabolised. The major metabolite is an inactive indole acetic acid derivative.

Half-life: Elimination: Approximately 2 hours. One study reported a terminal half-life of approximately 7 hours that became apparent about 12 hours after administration of multiple oral doses, but did not contribute substantially to the overall disposition of the medication.

Onset of action: Within 30 minutes.

Time to peak concentration: In serum (single 100 mg dose): Approximately 1.5 hours (range, 0.5 to 5 hours). The wide interindividual variability found in pharmacokinetic studies may be related to the appearance of multiple peaks in the concentration over time. Approximately 80% of the maximum value is achieved within 45 minutes.

Peak concentration: In serum (single 100 mg dose): Approximately 54 nanograms per ml; (0.13 micromoles/L) (range 26.7 to 137 nanograms per ml; 0.06 to 0.33 micromoles/L).

Time to peak effect: Relief of headache (i.e. moderate or severe pain being reduced to mild or no pain) - Single 100 mg dose: Within 2 hours in 50 to 75%, and within 4 hours in an additional 15 to 25% of patients.

Relief of associated symptoms (nausea, vomiting, photophobia, phonophobia)- Single 100 mg dose: Within 2 hours.

Duration of action: Return of migraine headache occurs within 24 to 48 hours in approximately 40% of patients who initially obtain a beneficial response to sumatriptan, i.e. after moderate or severe headache pain has been reduced to mild or no pain. Whether this represents development of a new migraine or breakthrough of a prolonged migraine after the effects of sumatriptan have worn off has not been established.

Elimination: Renal, via active renal tubular secretion, following hepatic metabolism. Approximately 80% of a dose is eliminated as metabolites. After oral administration, approximately 57% of a dose is eliminated in the urine (3% of the dose as unchanged sumatriptan, 35% as the indole acetic acid metabolite) and another 38% of the dose is eliminated in the faeces (9% as unchanged sumatriptan and 11% as the indole acetic acid metabolite). The effects of renal function impairment on clearance of sumatriptan have not been studied. Hepatic impairment produces an increase of 80% in plasma levels after oral dosing.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Hypromellose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 Years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Double foil (alu/alu) blister packs contained in a cardboard carton
Pack sizes: 2, 3, 4, 6, 12, 18 and 24

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Chanelle Medical,
Loughrea,
Co. Galway,
Ireland.

8 MARKETING AUTHORISATION NUMBER

PA0688/010/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 12th September 2008

10 DATE OF REVISION OF THE TEXT