IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0749/037/002
Case No: 2059497

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

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

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

Sumatriptan Teva 100mg 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 **30/04/2009**.

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

Each film-coated tablet contains 100 mg of sumatriptan (as sumatriptan succinate).

Excipients:
Each film-coated tablet contains 135.1 mg of lactose (as dry substance) as lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oblong shaped film-coated tablet debossed “100” on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute treatment of migraine attacks with or without aura.

4.2 Posology and method of administration

Sumatriptan should not be used prophylactically.
Sumatriptan is recommended as monotherapy for the acute treatment of migraine and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).
Sumatriptan should be taken as early as possible after migraine pain has appeared. However, sumatriptan is equally effective when administered at a later time during the attack.
The following recommended dosages should not be exceeded.

Adults
The recommended dose for adults is a single dose of 50 mg. For some patients, 100 mg may be necessary.
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.

If the patient does not respond to the first dose of sumatriptan, another dose should not be taken for the same attack. Sumatriptan may be used to treat subsequent attacks.
If symptoms disappear with the first dose but recur, 1 or 2 additional doses may be taken within the next 24 hours, provided that there is a minimum interval of 2 hours between the doses and not more than 300 mg is taken during this period.

The tablets should be swallowed whole with water.

Children (under 12 years of age)
Sumatriptan is not recommended for use in children below 12 as it has not been studied in children.

Adolescents (12 to 17 years of age)
The efficacy of sumatriptan in adolescents could not be demonstrated in the clinical studies performed in this age group. Therefore, use in adolescents is not recommended (see section 5.1).

Elderly
There is limited experience of the use of sumatriptan in patients over the age of 65 years. The pharmacokinetics of the medicinal product in elderly patients has not been studied enough. The use of sumatriptan in patients over 65 years is not recommended until more clinical data are available.

Hepatic insufficiency
Patients with mild to moderate liver insufficiency: low doses of 25-50 mg should be considered for patients with mild to moderate liver impairment.

Renal insufficiency
See section 4.4.

4.3 Contraindications

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

Sumatriptan must not be given to patients who have had myocardial infarction or who have ischaemic heart disease, Prinzmetal's variant angina/spasms of the coronary artery or peripheral vascular disease or patients who have symptoms or signs consistent with ischaemic heart disease.

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

The use of sumatriptan in patients with moderate or severe hypertension or mild uncontrolled hypertension is contraindicated.

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

Concurrent administration of ergotamine or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine1 (5-HT1) receptor agonist with sumatriptan is contraindicated (see section 4.5).

Concurrent administration of sumatriptan with reversible (e.g. moclobemide) or irreversible (e.g. selegiline) monoamine oxidase inhibitors (MAOIs) is contraindicated.

Furthermore, sumatriptan must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

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

Sumatriptan is not indicated for use in 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 taken into account that migraine patients may have an increased risk to be affected by certain cerebrovascular disorders (e.g. CVA, TIA).

Following administration, sumatriptan can be associated with transient symptoms such as chest pain and sensations of

tightness which may be intense and may also be felt in the throat area (see section 4.8.). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan are to be given and an appropriate evaluation must be carried out.

Sumatriptan should not be prescribed to patients with risk factors for ischaemic heart disease, including diabetics, heavy smokers or patients on nicotine substitution therapy without prior cardiovascular evaluation (see section 4.3.). Special consideration should be given to post-menopausal women and to men over the age of 40 who have 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.

There have been rare post-marketing reports describing patients with weakness, hyper-reflexia and lack of co-ordination after using selective serotonin re-uptake inhibitors (SSRI) and sumatriptan. If the simultaneous use of sumatriptan and SSRIs is clinically justified, appropriate observation of the patient is advised (see section 4.5).

Sumatriptan should be administered with caution to patients with conditions which may affect the absorption, metabolism or excretion of the medicine, such as impaired hepatic or renal function.

Sumatriptan should be administered 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 following administration of sumatriptan. The strength of the reaction ranges from a skin reaction to anaphylaxis. Evidence of cross-allergy is limited, but sumatriptan should nevertheless be administered with caution to such patients.

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 MOH (medication overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 amount of patients.

The recommended dosage should not be exceeded.

Sumatriptan Film-coated Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 ergotamine-containing preparations or another triptan/5-HT1. 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 or another triptan/5-HT1 receptor agonist 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 or another triptan/5-HT1 receptor agonist before administering sumatriptan. Conversely it is advised to wait at least six hours following use of sumatriptan before administering an ergotamine-containing product and atleast 24 hours before administering another triptan/5-HT1 receptor agonist (see section 4.3).

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

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

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

4.6 Pregnancy and lactation

Post-marketing data from the use of sumatriptan during the first trimester 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 onperi- and postnatal development. However, embryofetal 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 fetus.

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 effect on the ability to drive and use machines have been performed.

Drowsiness 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 (≥ 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.

Clinical Trial Data

Nervous system disorders

Common: Tingling, dizziness, drowsiness.

Vascular disorders

Common: Transient increases in blood pressure arising soon after treatment. Flushing.

Gastrointestinal disorders

Common: Nausea and vomiting occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition.

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).

General disorders and administration site conditions

Common: Pain, sensations of heat, 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).

Uncommon: Feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).

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 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. Nystagmus, scotoma, tremor, dystonia.

Eye disorders

Very rare: 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

Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see sections 4.3 and 4.4).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal disorders

Very rare: Ischaemic colitis

Musculoskeletal, connective tissue and bone disorders

Very rare: Neck stiffness.

4.9 Overdose

Patients have received up to 12 mg of sumatriptan, as a single, subcutaneous injection without significant undesirable effects. With subcutaneous doses exceeding 16 mg and oral doses exceeding 400 mg, no other adverse effects have been observed other than those mentioned in section 4.8.

In cases of overdose, the patient must be monitored for at least 10 hours and, if necessary, standard supportive treatment must be given.

There is no information on the effect of haemodialysis or peritoneal dialysis on plasma sumatriptan concentrations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics: antimigraine preparations: selective serotonin (5-HT_1) receptor agonists

ATC code: N02CC01

Sumatriptan is a specific and selective agonist of the vascular 5-hydroxytryptamine$_1$ receptor, with no effect on other 5-HT receptor sub-types. Receptors of this type have mainly been found in cranial blood vessels. In animals, sumatriptan selectively causes vasoconstriction in the circulation of the carotid artery, which supplies blood to extracranial and intracranial tissues such as the meninges. The dilatation of these vessels is thought to be the underlying mechanism of migraine in humans. The results of tests on animalsindicate that sumatriptan also inhibits the activity of the trigeminal nerve. Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine-inhibiting effect of sumatriptan in humans.

The clinical response begins about 30 minutes after oral administration of a 100 mg dose.

Doses of 25 mg-100 mg have been shown to be more effective than placebo in clinical trials but 25 mg is statistically significantly less effective than 50 mg and 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.

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 to 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 12-17 years was similar to that reported from studies in the adult population.

5.2 Pharmacokinetic properties

Following oral administration, sumatriptan is rapidly absorbed, 70 % of maximum concentration is achieved after 45 minutes. The mean peak concentration in plasma after a dose of 100 mg is 54 ng/ml. The mean absolute oral bioavailability after oral administration is 14 % partly due to presystemic metabolism and partly due to incomplete absorption. The elimination half-life is approximately 2 hours.

Binding to plasma protein is low (14 – 21 %) and the mean volume of distribution is 170 litres. The mean total clearance is approximately 1160 ml/min and the mean renal clearance is approximately 260 ml/min. The non-renal clearance accounts for about 80 % of the total clearance, which indicates that sumatriptan is primarily eliminated by metabolism. In patients with hepatic insufficiency, pre-systemic clearance after oral administration is reduced, resulting in an increase in the plasma levels of sumatriptan. The main metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine as free acid and glucuronide conjugate. It possesses no known 5-HT_1 or 5-HT_2 activity. Minor metabolites have not been identified. Migraine attacks do not appear to have a significant effect on the pharmacokinetics of orally administered sumatriptan.

5.3 Preclinical safety data

Experimental studies on acute and chronic toxicity gave no evidence on toxic effects in range of human therapeutic doses.

In a rat ferfility study, a reduction in the success of insemination was seen at exposures sufficiently in excess of the maximum human exposure.

In rabbits, embryolethality, without marked teratogenic defects, was seen. The significanceof these findings for humans

is unknown.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Croscarmellose sodium
Cellulose, microcrystalline
Silica colloidal anhydrous
Magnesium stearate
Coating – Opadry II 33G28707 white
Hypromellose E464
Titanium dioxide E171
Lactose monohydrate
Macrogol 3000
Glycerol triacetate

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

Transparent or white opaque PVC/PVdC aluminium blisters.

Blisters of 2, 3, 4, 6, 12, 18, 30 and 50 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/37/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 October 2007

Date of last renewal: 30 April 2009

10 DATE OF REVISION OF THE TEXT

April 2010