IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1063/022/001
Case No: 2038944

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

Niche Generics Limited

1 The Cam Centre, **Wilbury Way**, **Hitchin**, **Hertfordshire SG4 0TW**, **United Kingdom**

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

Sumatriptan Niche 50 Milligram 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 **31/10/2007** until **13/07/2011**.

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 Niche 50mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablets contains 50mg of Sumatriptan (as succinate)

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Sumatriptan Niche 50 mg Film-coated tablets are light pink, film-coated, oblong, biconvex tablets with a scoreline.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sumatriptan Niche tablets are indicated for the acute relief of migraine attacks, with or without aura including the acute treatment of menstrually associated migraine.

4.2 Posology and method of administration

The tablets should be swallowed whole with water.

Sumatriptan is recommended as monotherapy for the acute treatment of 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.

Adults only:

Sumatriptan Niche tablets are indicated for the acute intermittent treatment of migraine. It should not be used prophylactically.

It is advisable that sumatriptan be given as early as possible after the onset of an attack of migraine but it is equally effective at whatever stage of the attack it is administered.

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 Niche tablets, a second should not be taken for the same attack. Sumatriptan Niche tablets may be taken for subsequent attacks.

Patients who respond initially but whose migraine returns may take further doses in the next 24 hours provided that there is a minimum interval of two hours between doses. A maximum dose of 300 mg in any 24 hour period should not be exceeded.

Children (under 18 years):

The safety and effectiveness of Sumatriptan Niche tablets in children and adolescents under 18 years has not been established.

Elderly (more than 65 years):

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 Niche tablets 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 myocardial infarction or have ischemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or sign consistent with ischemic heart disease.

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

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

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

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated. (See *Section 4.5 – Interactions*).

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated. Sumatriptan should 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 where there is a clear diagnosis of migraine

Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.

The recommended doses of sumatriptan should not be exceeded. As with other migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.

It should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischemic attack).

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 – Undesirable Effects*). Where such symptoms are thought to indicate ischemic heart disease, no further doses of sumatriptan should be given and appropriate evaluation should be carried out.

Sumatriptan should not be prescribed for patients with risk factors for ischaemic heart disease such as diabetes, heavy smokers or patients on nicotine substitution therapy without prior cardiovascular evaluation (See *Section 4.3).*

There have been a number of fatalities from ventricular fibrillation and myocardial infarction.
The recommended dose of Sumatriptan Niche should not be exceeded.

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).

Special consideration should be given to postmenopausal women and males over 40 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.

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 post-marketing reports describing patients with weakness, hyper-reflexia, and in-coordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

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

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.

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

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Sumatriptan has the potential to interact with MAOIs, ergotamine and derivatives of ergotamine. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contra-indicated. (see also *Section 4.3 – Contraindications*).

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 contra-indicated (see *Section 4.3 – Contraindications*). Rarely, an interaction may occur between sumatriptan and SSRI's (see *Section 4.4 – Special Warnings and Special Precautions for Use*).

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 on peri- and postnatal development. However, embryo foetal viability might be affected in the rabbit (see *Section 5.3 – Preclinical Safety Data*).

Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

It has been demonstrated that following subcutaneous administration, sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with Sumatriptan Niche tablets. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

4.8 Undesirable effects

General

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat; pain, sensations of tingling, heat, heaviness, pressure or tightness. The following symptoms are mild to moderate in intensity and transient: flushing, dizziness and feelings of weakness.

Fatigue and drowsiness have been reported.

Cardiovascular

Hypotension, bradycardia, tachycardia, palpitations.

Transient increases in blood pressure arising soon after treatment have been recorded. In extremely rare cases, serious coronary events have been reported which have included cardiac arrhythmias, ischaemic ECG changes, coronary artery vasospasm or myocardial infarction. (see *Section 4.3 – Contraindications* and *Section 4.4 – Special Warnings and Special Precautions for Use*).

There have also been rare reports of Raynaud's phenomenon and ischaemic colitis.

Gastrointestinal

Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

CNS

There have been rare reports of seizures following use of sumatriptan. 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.

Eye Disorders

Patients treated with Sumatriptan Niche rarely exhibit visual disorders like flickering and diplopia. Additionally, cases of nystagmus, scotoma and reduced vision have been observed. Very rarely, loss of vision has occurred, which is usually transient. However, visual disorders may also occur during a migraine attack itself.

Hypersensitivity/skin

Hypersensitivity reactions ranging from cutaneous hypersensitivity to, in rare cases, anaphylaxis.

Laboratory values

Minor disturbances in liver function tests have occasionally been observed.

4.9 Overdose

Doses in excess of 400 mg 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics: Selective 5-HT1 receptor agonists.
ATC code: N02C C01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine1 (5HT1D) receptor agonist with no effect on other 5HT receptor (5-HT2-5-HT7) subtypes. The vascular 5-HT1D 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 of 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 around 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

Following oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After 100 mg dose, the maximum plasma concentration is 54 ng/ml. Mean absolute oral bioavailability is 14% partly due to presystemic metabolism and partly due to incomplete absorption. The elimination phase half-life is approximately 2 hours, although there is an indication of a longer terminal phase.

Plasma protein binding is low (14-21%), mean volume of distribution is 170 litres. Mean total plasma clearance is approximately 1160 ml/min and the mean renal plasma clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the 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. The pharmacokinetics of oral sumatriptan do not appear to be significantly affected by migraine attacks.

In a pilot study, no significant differences were found in the pharmacokinetic parameters between the elderly and young healthy volunteers.

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 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 embryo lethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Talc
Colloidal anhydrous silica

Film coat
Hypromellose
Macrogol
Talc
Titanium dioxide (E171)
Lake with cochineal red (E124-mixture of hydroxide and 1-(4-sulpho-1-naphtylazo)-2-naphthol-6,8-disulphonic acid)
Triethyl citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

Polyamide/Alu/PVC/Alu blister packs in a cardboard carton with Patient Information leaflet. Pack sizes may include 1, 2, 4, 6, 12 or 18 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited
1 the Cam Centre
Wilbury Way
Hitchin
Herts SG4 0TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1063/22/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 14th July 2006

10 DATE OF REVISION OF THE TEXT

October 2007