SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sumatriptan (as succinate).

Excipient with known effect
Lactose monohydrate (tablet core) 163.00 mg per film-coated tablet

Each tablet contains 100 mg sumatriptan (as succinate).

Excipient with known effect
Lactose monohydrate (tablet core) 93.00 mg per film-coated tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Pink, round, film-coated tablets debossed “SU50” on one side “G” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sumatriptan is indicated for the acute relief of migraine attacks, with or without, aura, including acute migraine attacks associated with menstruation.
Sumatriptan should only be used where there is a clear diagnosis of migraine.

4.2 Posology and method of administration

Posology
Adults
Sumatriptan is indicated for the acute intermittent treatment of migraine. It should not be used prophylactically. The recommended dose of sumatriptan should not be exceeded.

It is advisable that sumatriptan be given as early as possible after the onset of a

migraine attack, but it is equally effective at whatever stage of the attack it is administered.

The recommended dose of oral sumatriptan is a 50 mg tablet. Some patients may require 25 mg or 100 mg. The tablet cannot be divided into two equal doses; if necessary, the use of other medicinal product with the same active ingredient, dosage and pharmaceutical form available in divisible tablet should be considered. If the patient has responded to the first dose but the symptoms recur a second dose may be given provided that there is a minimum interval of two hours between the two doses. No more than 300 mg should be taken in any 24-hour period.

Patients who do not respond to the prescribed dose of sumatriptan should not take a second dose for the same attack. In these cases, the attack can be treated with paracetamol, acetylsalicylic acid or non-steroidal anti-inflammatory drugs. Sumatriptan may be taken for subsequent attacks.

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).

Paediatric population
The efficacy and safety of sumatriptan film-coated 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 film-coated 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 film-coated tablets in children 10 to 17 years of age is not recommended (see section 5.1).

Elderly (over 65 years of age)
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.

Hepatic impairment
Dosage adjustment is necessary in these patients (see sections 4.4 and 5.2).

Method of administration
The tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Sumatriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), 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 moderate and severe hypertension and mild uncontrolled hypertension is contraindicated.

Concurrent administration of reversible and irreversible monoamine oxidase inhibitors and sumatriptan is contraindicated. Sumatriptan tablets must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist or lithium with sumatriptan is contraindicated (see section 4.5).

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 opthalmoplegic migraine.

Before treating with sumatriptan, care should be taken to exclude potentially serious neurological conditions, e.g. cerebrovascular accident (CVA), transient ischaemic attack (TIA), if the patient presents with atypical symptoms or if they have not received an appropriate diagnosis for sumatriptan use.

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 appropriate evaluation should be carried out.

Sumatriptan should not be given to patients with risk factors for ischaemic heart disease, including those patients who are diabetics, 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 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 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).

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 which may affect significantly the absorption, metabolism or excretion of drugs, e.g. impaired hepatic (see section 5.2) or renal function (see section 5.2).

Patients with known hypersensitivity to sulfonamides 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*).

Sumatriptan should be used with caution in patients with epilepsy and/or 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).

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 medication.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Preparations containing ergotamine or other triptans/5-HT_1 receptor agonists may lead to prolonged vasospastic reactions. There is limited data relating to interactions with these preparations. The increased risk of coronary artery spasm is a theoretical possibility, therefore 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-HT_1 receptor agonist is not known. This will also depend on the doses and types 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-HT_1 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-HT_1 receptor agonist.

An interaction may occur between sumatriptan and monoamine oxidase inhibitors (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 nervous system imbalance 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 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, embryonic and foetal death may occur in rabbits (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. Somnolence and dizziness or other related symptoms either due to the migraine or treatment with sumatriptan may occur. This may influence the ability to drive and to operate machinery.

Caution is recommended for patients engaged in such activities.

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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), 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 anaphylactic reactions.

Psychiatric disorders
Not known: Anxiety.

Nervous system disorders
Common: Dizziness, somnolence, 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. Tremor, dystonia, nystagmus, visual field defect.

Eye disorders
Not known: Flickering, diplopia, reduced vision. Loss of vision including reports of permanent defects. However, visual impairment 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 pectoris, 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, dysphagia.

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).

Not known: Pain trauma activated, pain inflammation activated.

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

<u>Reporting of suspected adverse reactions</u>
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 the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of Overdose
Oral doses up to 100 mg were not associated with side effects other than those mentioned.

Treatment
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: Anti-migraine preparations, selective serotonin (5-HT_1) agonists, ATC Code: NO2CC01

Mechanism of action
Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine$_1$, (5-HT_{1D}) receptor agonist with no effect on the other 5-HT receptor (5-HT_2 – 5-HT_7) subtypes. The vascular 5-HT_{1D} 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 dilation 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 efficacy and safety
Following administration of 50 mg or 100 mg film-coated tablets, the onset of pain relief occurs after 30 and 20 minutes respectively in a small percentage of subjects and the percentage of subjects who responded to therapy, with pain relief occurring within two hours, progressively increasing to 67% and 72% of subjects, compared to 42% of subjects treated with a placebo. In a small percentage of patients, complete pain freedom occurred after 33 and 26 minutes respectively and the percentage continued to increase to 40% and 47% of subjects pain-free within 2 hours, compared to 15% of subjects treated with a placebo.

Paediatric population
A number of placebo-controlled clinical studies assessed the safety and efficacy of

oral sumatriptan standard tablets in over 650 child and adolescent migraineurs aged 10-17 years. These studies failed to demonstrate a statically significant difference in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in children and 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, 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 Cmax of sumatriptan increased by 15% following the administration of film-coated tablets with a meal with a high lipid concentration.

Distribution
Plasma protein binding is low (14-21%), mean volume of distribution is 170 litres.

Biotransformation
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 5-HT_1 or 5-HT_2 activity. Minor metabolites have not been identified.

Elimination
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/min and the mean renal plasma clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80% of the total clearance.

Pharmacokinetics in migraineurs
The pharmacokinetics of oral sumatriptan do not appear to be significantly affected by migraine attacks.

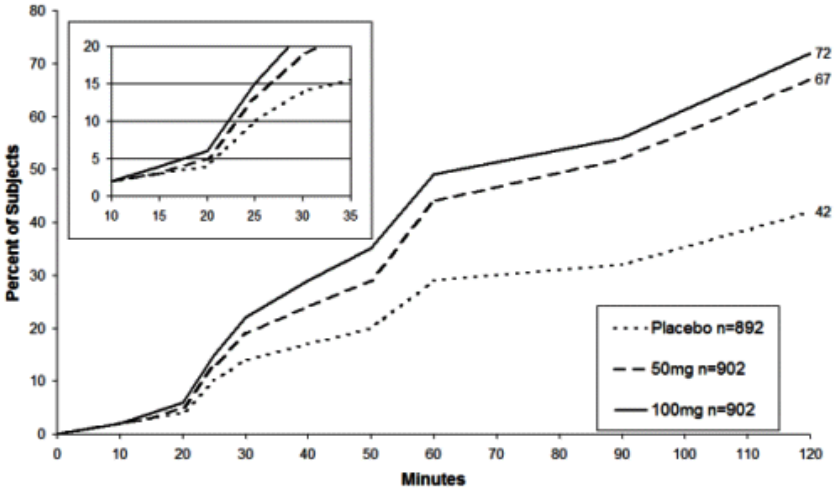
Special patient populations

Hepatic Impairment
Sumatriptan pharmacokinetics after an oral dose (50 mg) and a subcutaneous dose (6 mg) were studied in 8 patients with mild to moderate hepatic impairment matched for sex, age, and weight with 8 healthy subjects. Following an oral dose, sumatriptan plasma exposure (AUC and C_{max}) almost doubled (increased approximately 80%) in patients with mild to moderate hepatic impairment compared to the control subjects with normal hepatic function. There was no difference between the patients with hepatic impairment and control subjects after the s.c. dose. This indicates that mild to moderate hepatic impairment reduces presystemic clearance and increases the bioavailability and exposure to sumatriptan compared to healthy subjects.
Following oral administration, pre-systemic clearance is reduced in patients with mild to moderate hepatic impairment and systemic exposure is almost doubled.
The pharmacokinetics in patients with severe hepatic impairment have not been studied (see Section 4.3 and 4.4).

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

Clinical studies
The time of onset of the therapeutic effect of sumatriptan 50 mg and 100 mg film-coated tablets has been evaluated in adults in 2 randomised, double-blind, placebo-controlled studies, identical in design. Data from these studies was combined to obtain individual results for each endpoint. Overall, in 2 696 subjects with moderate to severe migraine pain, the time to pain relief and the time to pain freedom were reported in the groups treated with 50 mg, 100 mg sumatriptan and a placebo. The curves relating to the time to pain relief (defined as a reduction in pain severity from moderate or severe to mild or absent) were generated for sumatriptan and a placebo for a period of two hours after the start of treatment. The time interval of onset of pain relief was defined as the earliest time in which the statistical significance, compared to a placebo, was reached and then maintained in all subsequent times on the curve from 0 to 2 hours.
Pain freedom (defined as a reduction in the intensity of pain from severe or moderate to no pain) was evaluated using the same methodology (see Pharmacodynamic effects).
The percentage of subjects who achieved pain relief (Figure 1) or pain freedom (Figure 2) within 2 hours of treatment was significantly higher among the subjects who received sumatriptan (50 mg or 100 mg) compared to those who received a placebo ($p < 0.001$).

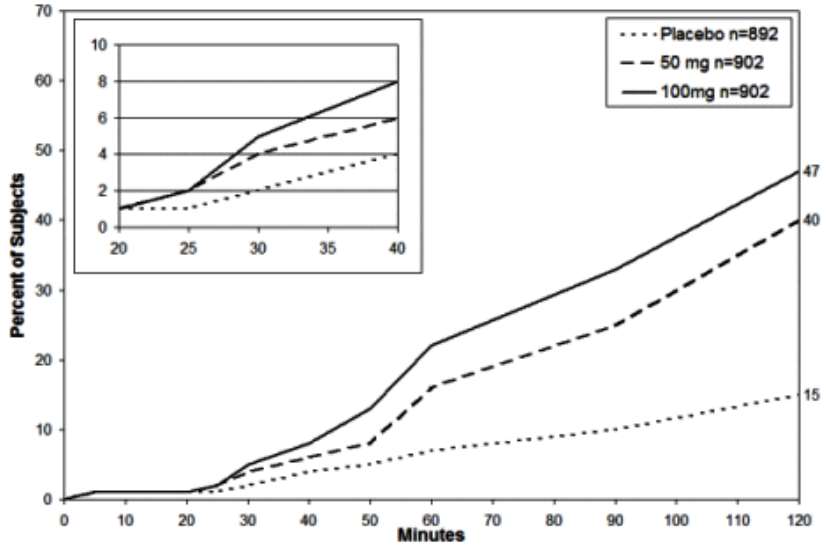
Figure 1: Time to pain relief in the two hours following treatment



Kaplan-Meier plot based on combined data from two studies, each of which provided evidence of efficacy. The box in Figure 1 shows the percentage of subjects with pain relief during the first 10–25 minutes following treatment.

From the analysis of the combined data, the time interval of the onset of pain relief for sumatriptan 50 mg and 100 mg film-coated tablets was 30 minutes and 20 minutes respectively. From this point in time onwards, the percentage of subjects who responded continued to increase, up to 67% and 72% of subjects who achieved pain relief, for 50 mg and 100 mg respectively, 2 hours after treatment, compared to 42% of subjects in the placebo group (Figure 1).

Figure 2: Time to pain freedom in the two hours following treatment



Kaplan-Meier plot based on combined data from two studies, each of which provided evidence of efficacy. The box in Figure 2 shows the percentage of pain-free subjects during the first 20–40 minutes following treatment.

From the analysis of the combined data, the time interval of the onset of pain freedom for sumatriptan 50 mg and 100 mg film-coated tablets was 33 minutes and 26 minutes, respectively. From this point in time onwards, the percentage of subjects who responded continued to increase, up to 40% and 47% of subjects pain-free, for 50 mg and 100 mg respectively, 2 hours after treatment, compared to 15% of subjects in the placebo group (Figure 2).

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 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 are approximately 150 times those in man by the oral route.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Tablet core</u>
Lactose monohydrate

Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Film coating
Titanium dioxide E171
Polydextrose E1200
Hypromellose E464
Triacetin E1518
Macrogol 8000
Iron oxide red E172
Iron oxide yellow E172

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

Polyamide-aluminium-PVC/ aluminium foil blister packs in a cardboard carton, containing either 2, 3, 4, 5, 6, 10, 12, 18, 20 or 24 tablets. Or blister unit dose in pack size 4 x 1 tablets.

Not all pack sizes may be marketed.

The blister pack may contain empty triangular shaped supporting knobs which do not contain any tablets. Only the round blister pockets contain tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,

EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 2006
Date of latest renewal: 30 August 2011

10 DATE OF REVISION OF THE TEXT

12/05/2023