SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg film coated tablet contains 140 mg sumatriptan succinate corresponding to 100 mg of sumatriptan.
Excipient: lactose monohydrate 143 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

100 mg: white to off-white, capsule shaped, biconvex, film coated tablet, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sumatriptan tablets are indicated for the acute treatment of migraine attacks, with or without aura. 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 migraine attack but it is equally effective at whatever stage of the attack it is administered.

The following recommended dosages should not be exceeded.

The recommended dose of oral sumatriptan is a single 50 mg tablet. Some patients may require 100 mg.

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 2 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 tablets 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).

Sumatriptan tablet is available in strengths of 50 and 100 mg.

Pediatric 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).

Elderly population (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
Patients with mild to moderate hepatic impairment: Low doses of 25–50 mg should be considered for these patients.

Renal impairment
Sumatriptan should be used with caution in patients with renal impairment.

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.
- The concomitant administration of ergotamine, or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist is contraindicated (see section 4.5).
- Concurrent administration of reversible (e.g. moclobemide) or irreversible (e.g. selegiline) monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated.

Sumatriptan must not be used within 2 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.

Before treating with sumatriptan, care should be taken to exclude potentially serious neurological conditions (e.g. CVA, 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 an 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 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 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 or an 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 drugs, e.g. impaired hepatic (Child Pugh grade A or B; see section 4.2 & 5.2) 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 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*).

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, the Lapp lactase deficiency or glucose-galactose- malabsorption should not take this medicine as it contains lactose.

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.

There are limited data on an interaction with preparations containing ergotamine or another triptan/5-HT_1 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-HT_1 receptor agonist is not known. This will also depend on the size of doses and the 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 (see section 4.3).

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 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).

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

Sumatriptan is excreted into breast milk, with average relative infant doses of < 4% following administration of a single dose of sumatriptan. Infant exposure can be minimised by avoiding breast-feeding for 12 hours after the treatment, during which time any breast milk expressed should be discarded.

There have been reports of breast pain and/or nipple pain following sumatriptan use in breastfeeding women (see section 4.8). The pain was usually transient and disappeared in 3 to 12 hours.

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 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, <1/1,000), very rare (<1/10,000) and 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. Tremor, dystonia, nystagmus, scotoma.

Eye disorders
Not known: Flickering, diplopia, reduced vision. Loss of vision including 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 syndrome.

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea

Gastrointestinal disorders
Common: Nausea and vomiting were 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, may be intense and can affect any part of the body including the chest and throat). Myalgia.
Not known: Neck stiffness, arthralgia.

Reproductive system and breast disorders
Rare: Breast pain

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 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.

Reporting of suspected adverse reactions
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 Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

There have been some reports of overdosage with sumatriptan tablets.

Symptoms
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.

Management
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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-migraine drugs, Selective serotonin ($5\text{-}HT_1$) agonists.
ATC code: N02CC01

Mechanism of action
Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine $1D_1$ ($5HT_{1D}$) receptor agonist with no effect on other 5HT receptor ($5HT_2$-$5HT_7$) 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 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 human.

Sumatriptan remains effective in treating menstrual migraine i.e. migraine without aura that occurs between 3 days prior and up to 5 days post onset of menstruation. Sumatriptan should be taken as soon as possible in an attack.

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

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

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 statistically 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

The pharmacokinetics of oral sumatriptan does not appear to be significantly affected by migraine attacks.

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 and it is reached in 2 hours. Mean absolute oral bioavailability is 14 % partly due to pre-systemic metabolism and partly due to incomplete absorption.

Distribution
Plasma protein binding is low (14 – 21 %) and the mean volume of distribution is 170 litres.

Biotransformation
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 $5HT_1$ of $5HT_2$ activity. Minor metabolites have not been identified.

Elimination
The elimination half-life is approximately 2 hours. Mean total plasma clearance is approximately 1160 ml/min and mean renal clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80 % of the total clearance, suggesting that sumatriptan is primarily cleared through oxidative metabolism mediated by monoamine oxidase A.

Elderly population

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

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 Cmax) 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 Contraindications and Section 4.4 Warnings and Precautions).

5.3 Preclinical safety data

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

In rat fertility study with doses well above the maximum doses used in humans, a reduction in successful inseminations was seen.

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

6.1 List of excipients

100 mg film coated tablet
Core of tablet
Lactose monohydrate
Hypromellose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Film coating
Hypromellose
Titanium dioxide (E 171)

6.3 Shelf life

2 years

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require special storage conditions.

6.5 Nature and contents of container

Individual tablets are packed in blisters (Al/Al).
Package sizes:
For 50mg: 4,6,12 and 18 tablets
For 100mg: 4, 6, 12 and 18 tablets
Not all package 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.
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited

Sage house, 319 Pinner Road,

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United Kingdom

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