Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan Arrow 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sumatriptan (as the succinate);
excipients: 83.70 mg Lactose, anhydrous.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off white, round biconvex tablet, embossed with 'SA' over '50' on one side and "  " on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sumatriptan tablets are indicated for the acute relief of migraine attacks, with or without aura.

4.2 Posology and method of administration

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

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3). If a patient fails to respond to a single dose of sumatriptan tablets there are no reasons, either on theoretical grounds or from limited clinical experience, to withhold products containing acetylsalicylic acid or non-steroidal anti-inflammatory drugs for further treatment of the attack.

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

Populations

Adults

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

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 there is a minimum interval of two hours between the two doses and no more than 300mg is taken in any 24 hour period.

The tablets should be swallowed whole with water.

Children (under 12 years of age)

Sumatriptan tablets are not recommended for use in children below 12 as sumatriptan tablets have not been studied in children.

Adolescents (12 to 17 years of age)

The efficacy of sumatriptan tablets in adolescents could not be demonstrated in the clinical studies performed in this age group. Therefore the use in adolescents 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 tablets in patients aged over 65 years is not recommended.

Hepatic insufficiency

Low doses of 25-50 mg should be considered for patients with mild to moderate liver impairment.

4.3 Contraindications

- Hypersensitivity to sumatriptan or to any of the excipients.
- 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-hydroxytriptamine $_1$(5-HT$_1$) receptor agonist is contraindicated. (See section 4.5).
- Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated.
- Sumatriptan tablets must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

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.

It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischaemic 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). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan tablets should be given and appropriate evaluation should be carried out.

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 also 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 Section 4.5).

Sumatriptan tablets 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.

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 tablets. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is limited but 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 medications.

The recommended dose of sumatriptan should not be exceeded.

Sumatriptan tablets 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 tablets 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.

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the 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

There is no evidence of interaction with propranolol, flunarizine, pizotifen or alcohol.

There are limited data on an interaction with ergotamine containing preparations or another triptan/5-HT1 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-HT1 receptor agonist is not known. This will also depend on the doses and type 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-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 at least 24 hours before administering another triptan/5-HT1 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).

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, embryofoetal 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.

Lactation

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. 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 reactions 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) and 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 anaphylaxis.

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 reports of 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 section 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.
Not known:	Diarrhoea.

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.
Not known:	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).

Investigations

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

Psychiatric disorders

Not known:	Anxiety.

Skin and subcutaneous tissue disorders

Not known:	Hyperhidrosis.

4.9 Overdose

Symptoms and Signs

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 undesirable adverse effects have been observed other than those mentioned in “section 4.8”.

Treatment

If overdosege occurs, the patient should be monitored for at least 10 hours and if necessary, 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-HT_1 receptor agonists.

ATC code: N02C C01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine$_1$ ($5HT_{1D}$) receptor agonist with no effect on other 5HT 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 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.

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 100mg oral dose.

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

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in approximately 600 adolescent migraineurs aged 12 – 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 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 occurring at 45 minutes. After 100mg dose, the maximum plasma concentration is 54ng/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 11 60ml/min and the mean renal plasma clearance is approximately 260ml/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 $5HT_1$ or $5HT_2$ 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 embryolethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Croscarmellose sodium
Magnesium stearate
Lactose, anhydrous

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 conditions.

6.5 Nature and contents of container

Polyamide/Aluminum/PVC/PVC/Aluminum/Polyamide blister packs (foil/foil cold form) containing 2, 3, 4, 6, 12, 18 or 24 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Ltd
Unit 2, Eastman Way
Stevenage
Hertfordshire, SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1130/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 20th March 2009

Date of last renewal: 14th May 2011

10 DATE OF REVISION OF THE TEXT

November 2011