

**SUMATRIPTAN 50MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 18909/0168**

**SUMATRIPTAN 100MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 18909/0169**

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LAY SUMMARY

The MHRA granted Arrow Generics Limited Marketing Authorisations (licences) for the medicinal products Sumatriptan 50mg Tablets (PL18909/0168) and Sumatriptan 100mg Tablets (PL 18909/0169) on 15th May 2006. These prescription only medicines (POM) are used for the relief of migraine attacks.

Sumatriptan Tablets contain the active ingredient sumatriptan succinate, which is used to reduce the temporary swelling of blood vessels, which is thought to cause migraine.

The data presented to the MHRA, pre licensing, demonstrated that Sumatriptan 50mg & 100mg Tablets are equivalent to the approved products, Imigran 50mg & 100mg Tablets. Sumatriptan Tablets can therefore be used interchangeably with Imigran Tablets.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Sumatriptan Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Sumatriptan 50mg Tablets (PL18909/0168) and Sumatriptan 100mg Tablets (PL 18909/0169) to Arrow Generics Limited on 15th May 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original products Imigran 50mg & 100mg Tablets.

The products contain the active ingredient sumatriptan and are indicated for the acute relief of migraine attacks, with or without aura, only when there is a clear diagnosis of migraine.

Sumatriptan is a specific and selective 5-Hydroxytryptamine₁ (5HT_{1D}) receptor agonist, which selectively constricts the carotid arterial circulation, preventing dilatation of and/or oedema formation in extracranial and intracranial tissues, which is thought to be the underlying mechanism of migraine in man.

PHARMACEUTICAL ASSESSMENT

I. GMP INSPECTION

A copy of the manufacturing authorisation issued by Health Canada dated 11/12/2002 is provided for the named finished product manufacturer, authorising the manufacture of pharmaceutical products. A GMP inspection letter has also been supplied. The applicant also lists 3 assembly sites. Manufacturing/assembly licences are provided for the EU packaging sites.

Five batch release sites are named in the application. These are acceptable as manufacturing authorisations from respective authorities are provided.

II. INTRODUCTION

These national abridged applications for sumatriptan tablets are made under EC Article 10.1 [formerly article 10.1(a) (iii)] of the Directive 2001/83/EC claiming essential similarity to the originator product, Imigran 50mg & 100mg Tablets authorised to GSK in the UK (PL 10949/0222 & 0231) licensed on 24/06/1994 and 01/08/1994, respectively. Hence the 10-year rule is complied with.

Sumatriptan is a vascular 5-HT₁ receptor agonist which acts to relieve migraine headache.

The active ingredient is the subject of a Ph Eur monograph.

MODULE 3 QUALITY

The drug substance is the subject of a PhEur monograph. The applicant has submitted a DMF for sumatriptan succinate. Letter of access naming the applicant and applications has been provided, dated March 2004. The source is currently under assessment in the UK in relation to another application.

Particle size analysis found particle size to be within the proposed limit. This is supported by the three batches of active substance tested. The finished product manufacturer tests each batch of drug substance according to the drug substance specification.

3.2.P DRUG PRODUCT

3.2.P.1 Composition

The qualitative composition of the proposed products are given in the table below.

Composition of proposed Tablets

Ingredient	Reference to Standard
Sumatriptan succinate	Ph Eur
Microcrystalline cellulose	Ph Eur
Croscarmellose sodium	Ph Eur
Magnesium stearate	Ph Eur
Purified water	Ph Eur
Mantle Coat	
Anhydrous lactose	PhEur
Microcrystalline cellulose	PhEur
Croscarmellose sodium	PhEur
Magnesium stearate	Ph Eur

Compliance with the latest edition of PhEur will be applied for all excipients referenced to Pharmacopoeial standard.

The 50mg and 100mg formulations are linearly related.

The tablets have two layers of different composition that are successively compressed. The mantle coat refers to the excipients in the second compression which fully coat the partially compressed core. The tablets fall within the definition of uncoated tablets.

3.2.P.2 Pharmaceutical development

Satisfactory trials were performed on formulation optimisation for the core and the mantle coat. Manufacturing process development has been detailed for both core tablet blend and mantle coat blend.

The dissolution method was developed using Apparatus II (paddles) of PhEur and various dissolution media were studied. The product rapidly released in all media. Comparative dissolution between UK, DE, SE, USA, CAN reference products and 4 test batches (2 of each tablet strength) as well as the test and reference products used in the bioequivalence study. Dissolution profiles between the UK reference product and the proposed products are comparable. The dissolution method was shown to be discriminatory.

The drug product is proposed to be included in blister packs. No compatibility studies on the packaging have been performed, however no incompatibility reactions were seen during the stability studies. This is acceptable.

3.2.P.3 Manufacture

Satisfactory batch formulae for maximum proposed batch sizes of Sumatriptan 50mg and 100mg tablets have been provided.

An outline of the manufacturing process and flow diagram have been provided in the dossier. The equipment used is specified.

In-process controls are adequate.

3.2.P.3.5 Process validation and/ or evaluation

The process has been qualified on one pilot batch of each tablet strength. Process validation protocols for the validation of production batches for the 50mg and 100mg tablets have been provided and are acceptable.

Data demonstrate that the critical stages in the manufacturing process are robust and well controlled.

A process validation protocol has been provided and will be applied to three consecutive production-scale batches of each strength at the proposed site of manufacture prior to commercial launch of the products.

Adequate controls are performed on the packaging.

The applicant proposes a 6 month holding period for tablets stored in bulk at 25°C/60%RH. Stability of the pilot batches in the proposed packaging was presented. The applicant will also perform formal transport studies on the first three production batches which includes temperature and humidity monitoring and testing of the batches on receipt to compare against the batch analysis pre transport. The date of expiry is calculated from the date of release of the batch, however should release exceed 30 days from the date of production the date of production will be defined as the date that the first step is performed combining the active ingredient with other ingredients and the expiry date will be calculated from this date.

3.2.P.4 Control of excipients

All excipients used are Ph Eur grade material and excipients are tested by the drug product manufacturer on receipt of each batch. Microcrystalline cellulose used is grade PH 101. The magnesium stearate used is vegetable grade, from a named supplier. A statement regarding compliance with EC No. 999/2001 has been provided by the supplier of the anhydrous lactose. A written declaration has been provided stating that the lactose anhydrous supplied is sourced exclusively from healthy animals in the same conditions as for milk sourced for human consumption, and that no other products of animal origin, with the exception of calf rennet, are employed in its manufacture.

The applicant has stated that all batches of excipients will be tested to the methods and specifications of the European Pharmacopoeia by the finished product manufacturer on receipt.

3.2.P.5 Control of drug product

3.2.P.5.1 Specification(s)

All specifications are the same at release and shelf life.

All non-compendial in house test methods have been adequately described. Methods used for assay, dissolution and determination of related substances have been adequately validated.

Batch analysis data have been presented for pilot batches of both strengths. These batches have been manufactured using the proposed drug substance source. Full batch analyses and certificates of analysis have been provided for all batches.

3.2.P.6 Reference Standard

Working standards for impurities are either sourced from the active substance manufacturer or obtained from PhEur. These have been supported by Certificates of Analysis. All working standards will be qualified directly against the primary pharmacopoeial reference standard.

3.2.P.7 Container closure system

The bulk tablets are stored in a polyethylene bag contained in a round HDPE container with a HDPE snap-on closure. Specifications for these packaging materials have been provided. The drug product is packaged in a foil blister comprising polyamide/aluminium/PVC/PVC/aluminium/polyamide blister packs. The pharmaceutical specification and certificate of analysis from the packaging material manufacturer have been supplied for the polyamide/aluminium/PVC packaging material.

Proposed pack sizes are 2,3,6,12,18 or 24 tablets.

Satisfactory finished product manufacturer's acceptance specifications and test procedures have been provided. The applicant states that non-routine or reduced testing may be applied by the finished product manufacturer or contract packaging facility following successful supplier qualification. The finished product manufacturer tests each batch of the packaging materials on receipt on description, identification (IR), thickness and width.

The adhesive lacquer is in compliance with BgVV recommendation XXVII and FDA 21 CFR 175.105 and the PVC is in line with EC Directive 90/128/EEC and PhEur. Confirmation has been provided that all packaging materials that come into direct contact with the proposed product comply with European Directive 90/128/EEC with respect to their suitability for contact with food.

3.2.P.8 Stability

The proposed shelf life: 2 years, with no special storage conditions.

Stability data have been presented for the pilot scale batches presented in batch analysis. Specifications are the same as at release, however identification and uniformity of mass are not performed. This is acceptable. All batches were stored at accelerated and long term conditions in line with ICH guidelines. Tablets were stored in the proposed foil/foil blisters and bulk container (polyethylene bags within a HDPE container). On the basis of real time data provided, the maximum holding period of 6 months is proposed for the bulk tablets in

the bulk pails. This is acceptable. The analytical methods used are the same as those proposed during release testing of the product.

All results remained within specification in the data presented at real time and accelerated conditions. No significant changes in any of the parameters were observed under real time or accelerated conditions.

A commitment has been provided to place the first three commercial batches of each strength on stability studies.

MODULE 1

1.2/ 1.3 Application form(s), Summary of Product Characteristics, Labelling & Package Leaflet

The MAA forms, SPC, labelling and leaflet are satisfactory.

1.4 Information about the Experts

1.4.1 Information about the Expert - Quality

A signed statement has been provided that the expert has performed the duties set out in Article 2 of the Council Directive 75/319/EEC in accordance with Part IC of Annex to Council Directive 75/318/EEC. The statement was signed by an Independent Regulatory Consultant and a CV was supplied.

1.5 Specific requirements for different types of applications

Bioavailability and Bioequivalence

A bioequivalence study has been performed between reference Imigran UK, and test product Sumatriptan 100mg tablets. Bioequivalence was demonstrated for the 100mg Tablets where the 90% confidence intervals for sumatriptan C_{max} , $AUC_{(0-inf)}$ and $AUC_{(0-t)}$ were within the accepted range 0.80- 1.25.

Blood plasma levels of sumatriptan versus time was assessed using a validated method.

MODULE 2

2.3 Quality Overall Summary

The quality overall summary is an accurate reflection of the data provided.

PHARMACEUTICAL RECOMMENDATION

Marketing Authorisations may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION / BACKGROUND

These comprise abridged National Marketing Applications for Sumatriptan 50 & 100 mg tablets made under EC Article 10.1 [formerly article 10.1 (a)(iii), first paragraph]. The proposed legal status is POM.

The reference medicinal products are Imigran 50 & 100 mg Tablets (PL 10949/0222 & 0231, GlaxoSmithKline, UK - granted 24 Jan 1994 and 01 August 2004).

Each tablet contains 70 or 140 mg of sumatriptan succinate equivalent to 50 or 100 mg of sumatriptan respectively.

Sumatriptan is a selective 5-HT₁ receptor agonist used in the treatment of migraine.

2. INDICATIONS

The proposed indication section in the SPC is:

“Therapeutic indications

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

Medical Assessor’s Comment:

This is the same as the text in the reference products SPC.

3. DOSE & DOSE SCHEDULE

The proposed dosage recommendations are:

“Posology and method of administration

Adults

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

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

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

Patients who do not respond to the prescribed dose should not take a second dose for the same attack. Sumatriptan Tablets may be taken for subsequent attacks.

Sumatriptan Tablets are 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 Tablets 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.

The tablets should be swallowed whole with water.

Children (Under 18 years of age)

The safety and effectiveness of Sumatriptan Tablets in children has not yet been established

Elderly (Over 65 years of age)

Experience of the use of Sumatriptan Tablets 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.”

Medical Assessor’s Comments:

These are the same as in the reference product’s SmPC.

4. TOXICOLOGY

The pharmaco-toxicological expert is a Consultant Toxicologist whose CV indicates appropriate qualifications and experience.

The SPC sections on pregnancy and lactation (4.6) and preclinical safety data (5.3) are consistent with those of the reference product.

5. CLINICAL PHARMACOLOGY

5.1 PHARMACODYNAMICS

Pharmacotherapeutic group: Analgesics: migraine medicines; selective 5HT₁-receptor agonists

ATC-code: N02CC01

Sumatriptan is a specific and selective agonist of vascular 5-hydroxytryptamine₁ receptor.

This type of receptor has been found mainly in cranial blood vessels.

In animals, sumatriptan causes selectively vasoconstriction in the carotid arterial circulation that supplies blood to extracranial and intracranial tissues, such as the meninges. The dilatation of these vessels has been thought to be the underlying mechanism of migraine in humans. The results of animal studies show that sumatriptan also inhibits the activity of the trigeminal nerve. Both actions (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 10 – 15 minutes after a subcutaneous injection of 6mg, 15 minutes after intranasal administration of 20mg and about 30 minutes after an oral dose of 100mg or a rectal dose of 25mg.

Although the recommended oral dose of Sumatriptan is 50mg, the severity of migraine attacks varies both within and between patients. Doses of 25mg – 100mg have shown to be more effective than placebo in clinical trials but 25mg is statistically significantly less effective than 50mg and 100mg.

5.2 PHARMACOKINETICS

After a subcutaneous injection, the mean bioavailability of sumatriptan is high (96%) and the maximum concentrations in serum are achieved within 25 minutes. The mean peak concentration in serum following a subcutaneous dose of 6mg is 72ng/ml. The elimination half-life is approximately 2 hours. Following oral administration, sumatriptan is rapidly absorbed and 70% of the maximum concentration is achieved after 45 minutes. The mean peak concentration in plasma after a dose of 100mg is 54ng/ml. The mean absolute bioavailability after oral administration is 14%, partly due to presystemic metabolism and partly due to incomplete absorption.

Binding to plasma proteins is low (14 – 21%) and the mean distribution volume is 170 litres. The mean total clearance is approximately 1160ml/min and the mean renal clearance is approximately 260ml/min. The non-renal clearance accounts for about 80% of the total clearance, which indicates that sumatriptan is primarily eliminated by metabolism. The main metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine, where it is present as free acid and glucuronide conjugate. It possesses no known 5HT₁ or 5HT₂ activity. Minor

metabolites have not been identified. Migraine attacks do not seem to have a significant effect on the pharmacokinetics of orally administered sumatriptan.

Medical Assessor’s Comment:

The pharmacodynamics and pharmacokinetics are well established and the respective sections in the proposed SPC are satisfactory.

5.3 BIOEQUIVALENCE

Study SMA-P3-079 (Arrow Generic No AP022): A randomised, 2-way crossover, single dose, comparative bioequivalence study of sumatriptan 100mg tablets in healthy male and female volunteers in the fasting state.

Objective: To evaluate and compare the relative bioavailability, and therefore the bioequivalence of two formulations of sumatriptan after a single oral dose administration under fasting conditions.

Subjects: 30 +4 (spares) male and female volunteers, aged 18-40 years. One subject dropped out and was replaced.

Test: Sumatriptan succinate 100 mg film-coated tablets.

Reference: Sumatriptan succinate [Imigran] 100 mg film-coated tablets.

Duration of treatment: Single oral dose was administered under fasting conditions in each study period [from 10 hrs before dosing to 4 hrs after] – treatment phases were separated by a washout of 7 days [NB elimination half life is around 2 hrs.].

Blood sampling: prior to drug administration and at specified time intervals post dose.

Parameters: main absorption and disposition parameters using non-compartmental approach [AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , K_{el} , $T_{1/2el}$]. Descriptive safety data were recorded.

Statistical analyses: ANOVA will be performed on C_{max} , T_{max} , AUC_{0-inf} , AUC_{0-t} , K_{el} , $T_{1/2el}$; geometric confidence interval for C_{max} , AUC_{0-inf} , AUC_{0-t} based on ln-transformed data; T_{max} rank transformed.

Criteria for Bioequivalence: The 90% geometric confidence interval for the exponential of the difference between the test and the reference product for the ln-transformed parameter of the ratio (T/R) of least-squares means from ANOVA of the ln transformed C_{max} , AUC_{0-inf} , AUC_{0-t} should be between 80 and 125%.

Results: Comparative pharmacokinetics:

	Sumatriptan test	Imigran reference	Test/Ref Ratio	Test/Ref (90% CI)
AUC_{0-t} (ng/ml h)	239.61	245.13	97.75%	93.4% to 102.3%

AUC_{0-inf} (ng/ml h)	248.67	254.56	97.68%	93.5% to 102.1%
C_{max} (ng/ml)	54.02	56.65	95.36%	88.4% to 102.8%
T_{max} (h) median (CV)	1.25 (74.9)	1.50 (68.7)		
T_{1/2el} (h) median (CV)	2.24 (17.8)	2.35 (20.0)		

Conclusions: Both formulations were well tolerated with no relevant safety differences. The test product was accepted as bioequivalent in terms of rate and extent of absorption to the reference product.

The generic Sumatriptan Tablets contain the same active and inactive ingredients as the branded product Imigran Tablets. The formulation of the 50mg and 100mg strengths of these sumatriptan tablets are scaled and the ratio between the amount of active substance and excipients is the same.

The results for the 100mg tablet can be considered applicable to the 50mg tablet.

6. EFFICACY

No new clinical efficacy data have been submitted with this application. None are required. There is adequate experience for the sumatriptan over more than a decade of worldwide usage. A literature review has been provided in the clinical expert report.

7. SAFETY

The safety profile of sumatriptan as used for the proposed indications is well established and has been reviewed adequately in the clinical expert report.

8. EXPERT REPORT

A satisfactory clinical expert report has been submitted by an appropriately qualified Consultant Pharmaceutical Physician.

9. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory.

10. PATIENT INFORMATION LEAFLET

Satisfactory.

11. LABELLING

Satisfactory.

12. DISCUSSION.

These applications are satisfactory.

13. RECOMMENDATION

Marketing authorisations may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Sumatriptan 50mg & 100mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data have been supplied with these applications and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Sumatriptan Tablets and the originator products, Imigran Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference products.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's products and the innovator products are interchangeable. Clinical experience with sumatriptan is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 05/07/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 16/07/2004
3	Following assessment of the application the MHRA requested further information relating to the dossier on 07/03/2005, 09/08/2005 and 15/05/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 04/05/2005, 28/07/2005, 13/09/2005, 19/12/2005, 05/01/2006 and 15/05/2006.
5	The application was determined on 15/05/2006.

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**SUMATRIPTAN 50MG TABLETS
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50mg Tablets


2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sumatriptan (as the succinate); excipients: 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. Sumatriptan tablets should only be used where there is a clear diagnosis of migraine.

4.2 Posology and method of administration

Adults

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

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

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

Patients who do not respond to the prescribed dose should not take a second dose for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Sumatriptan tablets are 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 tablets 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.

The tablets should be swallowed whole with water.

Children and adolescents (Under 18 years of age)

Sumatriptan tablets have not been studied in children under 12 years of age. The available clinical trial data in adolescents (12 to 17 years of age) do not support the use of oral sumatriptan in this age group (see section 5.1). The use of sumatriptan tablets in children and adolescents is therefore not recommended.

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

- patients with a known hypersensitivity to sumatriptan or any of the tablet excipients.
- 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 sign consistent with ischaemic heart disease.
- patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

- patients with severe hepatic impairment.
- patients with moderate and severe hypertension and mild uncontrolled hypertension.
- concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated. (See section 4.4).
- concurrent administration of monoamine oxidase inhibitors 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.

The recommended doses 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 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 4.7). 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.

Sumatriptan tablets should not be given to patients with risk factors for ischaemic heart disease 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.

There have been rare post-marketing reports describing patients with weakness, hyper-reflexia, and incoordination 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 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 Johns wort (*Hypericum perforatum*).

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 with other acute migraine treatments, chronic daily headache/exacerbation of headache have been reported with overuse of sumatriptan, which may necessitate a medicinal product withdrawal

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. 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 contraindicated. (see section 4.3).

Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan tablets can be taken following any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hours have elapsed following administration.

Rarely, an interaction may occur between sumatriptan and SSRIs (see section 4.3).

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

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, 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.

It has been demonstrated that following subcutaneous administration sumatriptan is secreted into breast milk. Infant exposure can be minimized by avoiding breast feeding for 12 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 Tablets. Caution is recommended in patients performing skilled tasks, e.g. driving or operating 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, <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, connective tissue and bone 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. Tremor, dystonia.

Eye disorders

Very rare: Flickering, diplopia, reduced vision, nystagmus, scotoma. 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 section 4.3 and 4.4).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal

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 undesirable adverse effects have been observed 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 hemodialysis or peritoneal dialysis on plasma sumatriptan concentrations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics:0 Selective 5-HT₁ receptor agonists.

ATC code: N02C C01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine₁ (5HT_{1D}) receptor agonist with no effect on other 5HT receptor (5-HT₂-5-HT₇) 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.

Five 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 1160ml/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 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 embryoletality, 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, 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
Tel: 0207 612 7612
Fax: 0207 612 7620
Email: arrow@arrowgenerics.co.uk

8 MARKETING AUTHORISATION NUMBER(S)

PL 18909/0168

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2006

10 DATE OF REVISION OF THE TEXT

15/05/2006

**SUMATRIPTAN 100MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 18909/0169**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg sumatriptan (as the succinate); excipients: 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 '100' on one side and "D" 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. Sumatriptan tablets should only be used where there is a clear diagnosis of migraine.

4.2 Posology and method of administration

Adults

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

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

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

Patients who do not respond to the prescribed dose should not take a second dose for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Sumatriptan tablets are 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 tablets 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.

The tablets should be swallowed whole with water.

Children and adolescents (Under 18 years of age)

Sumatriptan tablets have not been studied in children under 12 years of age. The available clinical trial data in adolescents (12 to 17 years of age) do not support the use of oral sumatriptan in this age group (see section 5.1). The use of sumatriptan tablets in children and adolescents is therefore not recommended.

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.

4.4 Contraindications

- patients with a known hypersensitivity to sumatriptan or any of the tablet excipients.
- 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.
- patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- patients with severe hepatic impairment.

- patients with moderate and severe hypertension and mild uncontrolled hypertension.
- concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated. (See section 4.4).
- concurrent administration of monoamine oxidase inhibitors 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.

The recommended doses 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 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 4.7). 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.

Sumatriptan tablets should not be given to patients with risk factors for ischaemic heart disease 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.

There have been rare post-marketing reports describing patients with weakness, hyper-reflexia, and incoordination 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 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 Johns wort (*Hypericum perforatum*).

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 with other acute migraine treatments, chronic daily headache/exacerbation of headache have been reported with overuse of sumatriptan, which may necessitate a medicinal product withdrawal

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. 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 contraindicated. (see section 4.3).

Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan tablets can be taken following any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hours have elapsed following administration.

Rarely, an interaction may occur between sumatriptan and SSRIs (see section 4.3).

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

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, 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 foetus.

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.

4.7 Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with Sumatriptan Tablets. Caution is recommended in patients performing skilled tasks, e.g. driving or operating 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, <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, connective tissue and bone 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. Tremor, dystonia.

Eye disorders

Very rare: Flickering, diplopia, reduced vision, nystagmus, scotoma. 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 section 4.3 and 4.4).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal

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 undesirable adverse effects have been observed 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 hemodialysis or peritoneal dialysis on plasma sumatriptan concentrations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics:0 Selective 5-HT₁ receptor agonists.

ATC code: N02C C01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine₁ (5HT_{1D}) receptor agonist with no effect on other 5HT receptor (5-HT₂-5-HT₇) 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.

Five 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 1160ml/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 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 embryoletality, 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 precautions

6.5 Nature and contents of container

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

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

8 MARKETING AUTHORISATION HOLDER

Arrow Generics Ltd
Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ
United Kingdom
Tel: 0207 612 7612
Fax: 0207 612 7620
Email: arrow@arrowgenerics.co.uk

8 MARKETING AUTHORISATION NUMBER(S)

PL 18909/0169

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2006

10 DATE OF REVISION OF THE TEXT

15/05/2006

**SUMATRIPTAN 50MG & 100MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 18909/0168-9**

PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Sumatriptan 50 mg and 100 mg Tablets

Read this leaflet carefully before you start taking this medicine even if you have only collected a repeat prescription. This leaflet contains information about your medicine. This medicine has been prescribed for you personally and you should **NOT** pass it on to others. It may harm them, even if their symptoms are the same as yours. You may wish to keep this leaflet, as you may want to read it again. If you have further questions, please ask your doctor or your pharmacist.

Marketing Authorisation Holder: Arrow Generics Limited
Unit 2, Eastman Way, Stevenage,
Hertfordshire, SG1 4SZ

Manufacturer: Arrow Pharm (Malta) Ltd
HF 62, Hal Far Industrial Estate,
Hal Far, Malta

WHAT IS YOUR MEDICINE?

Your medicine is in the form of a tablet. The tablets are available in two strengths and each tablet contains either 50 mg or 100 mg of sumatriptan (as the succinate).

The 50mg tablets are white to off white, round biconvex tablets, embossed with 'SA' over '50' on one side and "S" on the other side.

The 100mg tablets are white to off white, round biconvex tablets, embossed with 'SA' over '100' on one side and "S" on the other side.

Each tablet also contains cellulose microcrystalline, croscarmellose sodium, magnesium stearate and anhydrous lactose.

Sumatriptan tablets are available in blister packs of 2, 3, 6, 12, 18 or 24 tablets.

Not all pack sizes may be marketed.

What is your medicine for?

Sumatriptan tablets belongs to a group of medicines called 5HT₁ receptor agonists.

Sumatriptan tablets are used for the treatment of migraine. The symptoms of migraine may be due to temporary swelling of blood vessels in the head. Sumatriptan tablets are believed to work by reducing the size of these blood vessels.

Your doctor has decided that this medicine is suitable for treating your illness. If you are not sure why you are on these tablets, ask your doctor.

Before you take Sumatriptan Tablets:

Tell your doctor if the answer is yes to any of the questions below:

- you are allergic to sumatriptan or any of the other ingredients in sumatriptan tablets or to medicines called sulphonamides
- you suffer from unexpected shortness of breath, or from pain or tightness in the chest (which may or may not spread to your jaw or upper arms)
- you have any of the following medical conditions: heart disease such as heart failure, angina or coronary thrombosis (heart attack), high blood pressure, disease of the liver or kidneys, epilepsy or brain disease
- you are taking any medicines for your migraine which contain ergotamine or ergotamine derivatives, such as ergotamine tartrate or methysergide maleate (if so, you should stop taking them at least 24 hours before taking sumatriptan tablets)
- you are taking any medicines on a doctor's prescription for the treatment of depression such as lithium, MAOIs or SSRIs (including citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), or if you have taken an MAOI in the last 2 weeks
- you are taking any medicines on a doctors prescription to help you lose weight, or for the treatment of epilepsy
- you are taking anything containing the herbal remedy St John's Wort (*Hypericum perforatum*). Taking this together with sumatriptan tablets may increase the likelihood of you suffering side effects
- you are pregnant, or likely to become pregnant, are breast feeding or have stopped having periods altogether
- you are a man over 40 years of age
- you have any risk factors for heart disease such as family history of heart disease; sugar diabetes; high blood cholesterol; if you are a regular cigarette smoker or if you are very over weight
- you have had a stroke or a TIA (transient ischaemic attack) – a mild and transient form of stroke
- you have a history of seizures

If the answer is yes to any of the above questions tell your doctor immediately.

Even if you do answer yes to some of the above questions your doctor may still want you to take sumatriptan tablets and will advise you about taking the medicine.

Sumatriptan tablets may cause drowsiness. If you are affected do not drive or operate machinery.

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

How to take your medicine?

Your medicine should only be taken by mouth. Swallow each tablet whole with water. Do not chew or crush them. Overuse of these tablets can cause headaches.

- The usual dose is one 50mg tablet at the first sign of a migraine attack, although it will still be effective if taken at a later stage. Some patients may need to take a dose of two 50mg tablets or one 100mg tablet – you should follow your doctor's instruction.
- If the first dose does not make your migraine better do not take any more tablets for this attack because it is unlikely that a second dose will work. In this instance sumatriptan tablets can be used for your next attack.
- If, after your first dose, your migraine goes away but then returns, you may take another dose, provided it is at least **two hours** since you took the first dose. **DO NOT TAKE MORE THAN 6 tablets** in any 24-hour period, which is 300 mg in total.

If you suffer from liver problems, your doctor may prescribe a reduced dose.

There is little experience of use of sumatriptan tablets in children under 18 years of age or those over 65 years of age. Sumatriptan tablets are therefore not usually prescribed for these age groups.

What if you take too many tablets?

Too many tablets at once can be dangerous. If you take too many tablets tell your doctor. If you are unable to contact your doctor go to your local hospital casualty department at once. Don't forget to take your tablets or patient information leaflet with you.

Do not take more tablets at once than your doctor told you.

What if you do not feel better?

If sumatriptan tablets do not ease your migraine, then you may take your usual 'pain killers', provided they do not contain ergotamine or its derivatives. Wait at least six hours after taking sumatriptan tablets before taking any medicines containing ergotamine or its derivatives.

Does your medicine cause undesirable effects?

Like all medicines your tablets may cause some undesirable effects. Most people taking this medicine find it causes no problems, however a few people may find that they have side effects. Undesirable effects include:

- sudden wheezing, fluttering or tightness in the chest
- swelling of eyelids, face or lips
- a skin rash such as red spots or hives (skin lumps)
- fits – usually in people with a history of epilepsy
- visual disturbances (although these may occur due to the migraine attack itself)

THESE SYMPTOMS MAY MEAN THAT YOU ARE ALLERGIC TO sumatriptan tablets. Do **NOT** take any more of the tablets unless your doctor tells you to do so.

There have also been **rare** reports of the following:

- Raynaud's phenomenon, which is a disease characterised by signs of paleness or a blue tinge to the skin and/or pain of the fingers, toes, ears, nose or jaw in response to cold or stress.

- Inflammation of the colon (part of the intestine), which may present as lower left-sided tummy pain and bloody diarrhoea.

If you experience any of these symptoms while taking sumatriptan tablets, contact your doctor as soon as possible.

Some people may experience the following symptoms, however they are not usually troublesome.

They may be intense but do not last long.

- Feelings of tingling, warmth, heaviness, pressure, tightness or sometimes pain in different parts of the body, including the chest or throat; although sometimes very strong they usually only last a few minutes. If they continue or are particularly severe (especially chest pain) tell your doctor immediately as there have been extremely rare reports of such problems being caused by heart attack. Do **NOT** take any more tablets; your doctor will decide if you should stop using them
- Dizziness, feeling of weakness, fatigue or flushing
- Feeling sick (nausea) or being sick (vomiting), although this is often part of the migraine attack
- Tiredness or sleepiness (important if you are driving or working a machine)

Other side effects include stiffness in the neck changes in blood pressure and heart rate.

If you have a blood test to check your liver function, sumatriptan tablets may affect your results.

If you feel unwell or have any other unusual discomfort you do not understand, it is important to tell your doctor as soon as possible.

Tell your doctor straight away if you get any of these effects, or any other discomfort you do not understand.

This treatment is for **YOU**. Do not give it to others. It may not suit them.

Where to keep your medicine

Keep all medicines out of the reach and sight of children.

There are no special storage instructions. However do not store your medicine anywhere too hot or too damp.

If you notice any visible signs of deterioration in the tablets, such as chipped, broken or discoloured tablets, take them to your pharmacist for advice before taking them.

Do not take this medicine after the date stamped on the pack.

Date of preparation: ,May 2006

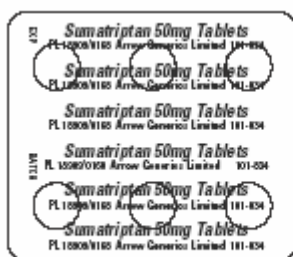
**SUMATRIPTAN 50MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 18909/0168**

LABELLING

CARTON



FOIL



**SUMATRIPTAN 100MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 18909/0169**

LABELLING

CARTON



FOIL

