Public Assessment Report

Sumatriptan 50mg Film-coated Tablets
Sumatriptan 100mg Film-coated Tablets

Sumatriptan succinate

PL 17907/0216
PL 17907/0217

Bristol Laboratories Limited

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific Discussion</td>
<td>3</td>
</tr>
<tr>
<td>Overall Conclusion And Risk Benefit/Analysis</td>
<td>10</td>
</tr>
<tr>
<td>Steps Taken During Assessment</td>
<td>11</td>
</tr>
<tr>
<td>Steps Taken After Assessment</td>
<td>12</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>13</td>
</tr>
<tr>
<td>Labels and Leaflet</td>
<td>35</td>
</tr>
</tbody>
</table>
Lay Summary

The MHRA granted Bristol Laboratories Ltd Marketing Authorisations (licenses) for the medicinal products Sumatriptan 50mg Film-coated Tablets (PL 17907/0216) and Sumatriptan 100mg Film-coated Tablets (PL 17907/0217) on the 24/03/2009.

These are prescription only medicines used in the treatment of migraine. Sumatriptan reduces increased blood flow to areas of the brain which is thought to be the major cause of migraine.

The drug products were demonstrated to be the same as the reference product Imigran® 50 and 100mg tablets, which were initially licensed in the UK in June 1994.
Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, granted Bristol Laboratories Ltd Marketing Authorisations for the medicinal products Sumatriptan 50mg and 100mg Film-coated Tablets (PL 17907/0216-7) on 24/03/2009. These medicines are available only with a prescription.

These were national standard abridged applications for Sumatriptan tablets (50 and 100mg) are made under EC Article 10.1 of the Directive 2001/83/EC, so called ‘generic applications’ with the reference products being Imigran® 50 and 100mg tablets, which were initially licensed in the UK in June 1994.

The products contain the active ingredient sumatriptan which is a specific and selective 5-Hydroxytryptamine₁ (5HT₁D) receptor agonist with no effect on other 5HT receptor (5-HT₂-5-HT₇) subtypes. Sumatriptan is indicated for the acute relief of migraine attacks, with or without aura.

The vascular 5-HT₁D receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and / or oedema formation in these vessels is though to be the underlying mechanism of migraine in man.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

The drug substance has a European Certificate of Suitability and the control of the active substance is as per the Certificate of Suitability.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active sumatriptan is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated with a retest period of 6 months.
DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients listed below:

- Lactose monohydrate
- Microcrystalline cellulose (Avicel PH 101)
- Microcrystalline cellulose (Avicel PH 200)
- Pregelatinized starch (Starch 1500)
- Croscarmellose Sodium
- Magnesium Stearate
- Hypermellose
- Titanium Dioxide
- Purified Talc
- Macrogol 6000
- Purified water

All the excipients are commonly used in the pharmaceutical industry and most of them are used in the reference product. All components of the product have monographs in the Ph. Eur with the exception of the colorants (ferric oxide red and ferric oxide yellow) which have monographs in the USP. The applicant has provided specifications and satisfactory Certificates of Analysis for all excipients. Lactose monohydrate is the only substance of animal origin and is produced from milk intended for human consumption.

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Tablets are packed in aluminium blisters strips of 0.025mm thickness. These materials are the same used in the stability studies and are considered acceptable for this product.
Satisfactory Certificates of Analysis in support of the proposed specifications from both vendor and finished product manufacturer have been provided and they are acceptable.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with the storage conditions “Store in the original package”.

**ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE**

A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

No pre-clinical data were submitted for these applications and none were required.
MEDICAL ASSESSMENT

Clinical Pharmacology

Pharmacodynamics
Sumatriptan is a specific and selective 5-Hydroxytryptamine₁ (5HT₁D) receptor agonist with no effect on other 5HT receptor (5-HT₂-5-HT₇) subtypes. Sumatriptan is indicated for the acute relief of migraine attacks, with or without aura.

The vascular 5-HT₁D receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and / or oedema formation in these vessels is though 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.

Pharmacokinetics
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.

Bioequivalence Study
Randomised, two-period, cross-over, bioequivalence study of Sumatriptan 100mg tablets versus Imigran 100mg tablets (GSK, UK) in healthy volunteers.

Study protocol
Fifty-six healthy male volunteers, aged 19-41 years, were included in this study. Three subjects were withdrawn from the study: one in Period II for personal reasons; and two in Period I due to adverse events; both subjects vomited following dosing. Fifty three subjects completed the study. Each subject received a single dose (100mg tablet) of one of the Sumatriptan formulations. For each subject there were 2 dosing periods, with a washout period of 7 or 8 days. A randomisation scheme was included in the report.
The reference is registered in the UK. The tablet was administered following a >10hr fast. 240ml water was administered to swallow the tablet. Standard meals were administered at 4, 8.25 and 13 hours post-dose. Blood samples for analysis were taken at 0, 0.16, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours following dosing. There followed a 7/8 day washout period before cross over and repeat.

AUC(0-t), AUC(0-inf), C\textsubscript{max}, t\textsubscript{max} and t\textsubscript{1/2} were calculated according normal standard procedures.

Statistical evaluation was performed for AUC(0-t), AUC\textsubscript{inf} and C\textsubscript{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

The study was conducted in accordance with GCP and GLP. The report is of good quality.

Table 5: Pharmacokinetic results between the test and reference products. Log transformed. ANOVA. 
n= 53 healthy male subjects.

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Test product (geometric means)</th>
<th>Reference product (geometric means)</th>
<th>Ratio Test/reference x 100</th>
<th>90% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{0-t}</td>
<td>332.12</td>
<td>328.65</td>
<td>101.05%</td>
<td>94.62 - 107.92%</td>
</tr>
<tr>
<td>AUC\textsubscript{0-\infty}</td>
<td>347.24</td>
<td>342.12</td>
<td>101.50%</td>
<td>95.62 - 107.74%</td>
</tr>
<tr>
<td>C\textsubscript{max}</td>
<td>75.62</td>
<td>81.21</td>
<td>93.12%</td>
<td>86.31 - 100.47%</td>
</tr>
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</table>

The 90% confidence intervals for the log-transformed parameters C\textsubscript{max}, AUC\textsubscript{0-t} and AUC\textsubscript{0-\infty} for sumatriptan are within the range 80 - 125%. Therefore, the test and reference products may be considered bioequivalent.

There were no serious adverse events reported. There were no clinically significant changes in the post study evaluations of haematology and biochemistry.

The claim that bioequivalence has been demonstrated is endorsed.

**Efficacy**

No new data are submitted and none are required for this type of application.

**Safety**

No new data are submitted and none are required for this type of application.

**Expert Reports**

A satisfactory expert report is provided by an appropriately qualified individual.
Summary of Product Characteristics
A satisfactory SPC was arrived at during the assessment process.

Patient Information Leaflet and Labelling
Satisfactory Patient Information Leaflet and Labelling were arrived at during the assessment process.

Conclusion
Marketing Authorisations may be granted for these products.
Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Sumitriptan 50mg and 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.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

Bioequivalence has been demonstrated between the drug product and the reference product. No new or unexpected safety concerns arise from these applications.

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

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.
### Steps Taken During Assessment

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<tr>
<td>1</td>
<td>The MHRA received the application on 18/05/2006.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 08/08/2006.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 09/08/2006 and 20/09/2007 on the medical assessment on 10/12/2008.</td>
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<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 06/09/2007 and 08/02/2008 on the medical assessment on 03/02/2009.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 24/03/2009.</td>
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Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg Sumatriptan base as the succinate salt. Also contains lactose monohydrate

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

Peach coloured, capsule shaped, biconvex film-coated tablets with ‘BL’ embossing on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sumatriptan is indicated for the acute relief 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

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

The recommended dose of oral Sumatriptan 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 of Sumatriptan tablets should not take a second dose for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Sumatriptan tablet is recommended as monotherapy for the acute treatment of migraine and should not be given concomitantly with other acute migraine therapies. If a patient fails to respond to a single dose of Sumatriptan tablet 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 tablet should be swallowed whole with water.

**Children (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)**

Experience of the use of Sumatriptan tablet 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.

**Route of administration:**

Oral

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4.3 **Contraindications**

Hypersensitivity to any component of the preparation.
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 sign 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 tablet 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-hydroxytryptamine₁ (5-HT₁) receptor agonist with sumatriptan is contraindicated. (See Section 4.5)

Concurrent administration of monoamine oxidase inhibitors and sumatriptan tablet is contraindicated.

Sumatriptan tablet must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Sumatriptan should only be used where there is a clear diagnosis of migraine.

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

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

It should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient 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 should be given and appropriate evaluation should be carried out.
Sumatriptan 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 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 serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs).

If concomitant treatment with sumatriptan tablet and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised.

Sumatriptan should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of drugs, e.g. impaired hepatic or renal function. A 50mg dose should be considered in patients with hepatic impairment.

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 tablet in these patients.

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

As with other acute migraine treatments, chronic daily headache/ exacerbation of headache have been reported with overuse of Sumatriptan, which may necessitate a drug withdrawal.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
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 monoamine oxidase inhibitors (MAOIs), ergotamine and derivatives of ergotamine. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contra-indicated (See also section 4.3).

There are limited data on an interaction with preparations containing ergotamine 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 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-HT1 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-HT1 receptor agonist.

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 Pregnancy and lactation

Post-marketing data from the use of sumatriptan tablet 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 tablet in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on perinatal and postnatal development. However, embryofoetal viability might be affected in the rabbit (see section 5.3). Administration of sumatriptan tablet 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 tablet is excreted 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

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 events are listed below by system organ class and frequency [4]. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000) and very rare (<1/10000) including isolated reports.

Clinical Trial Data

Nervous System Disorders
Common: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoesthesia.

Vascular Disorders
Common: Transient increases in blood pressure arising soon after treatment. Flushing.

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.

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).

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). 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, nystagmus, scotoma.

Eye disorders
Very rare: 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
Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see Contraindications, Warnings and Precautions).

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

There have been some reports of overdosage with Sumatriptan Tablets. Doses in excess of 400mg orally were not associated with side effects other than those mentioned.

If overdosage occurs, the patient should be monitored for at least ten hours and standard supportive treatment applied as required.
It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of Sumatriptan tablet.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: N02CC01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine1 (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 though 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 relevant differences 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 embryo lethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose (Avicel PH 101)
Microcrystalline cellulose (Avicel PH 200)
Pregelatinized starch (Starch 1500)
Croscarmellose Sodium
Magnesium Stearate
Hypermellose
Titanium Dioxide E171
Purified Talc
Macrogol 6000
Ferric oxide red E172
Ferric oxide yellow E172
Purified water

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

Alu / Alu blister, pack sizes of 2, 6, 12 tablets.

6.6 Special precautions for disposal

No special requirements.
7 MARKETING AUTHORISATION HOLDER

BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

17907/0216

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/03/2009

10 DATE OF REVISION OF THE TEXT

24/03/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100mg Sumatriptan base as the succinate salt. Also contains lactose monohydrate.

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

White, capsule shaped, biconvex film coated tablet with “BL” embossing on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sumatriptan is indicated for the acute relief 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

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

The recommended dose of oral Sumatriptan 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 of Sumatriptan tablets should not take a second dose for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Sumatriptan tablet is recommended as monotherapy for the acute treatment of migraine and should not be given concomitantly with other acute migraine therapies. If a patient fails to respond to a single dose of Sumatriptan tablet 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 tablet should be swallowed whole with water.

**Children (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)**

Experience of the use of Sumatriptan tablet 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.

**Route of administration :**

Oral

4.3 **Contraindications**

Hypersensitivity to any component of the preparation.
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 sign 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 tablet 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-hydroxytryptamine₁ (5-HT₁) receptor agonist with sumatriptan is contraindicated. (See Section 4.5)

Concurrent administration of monoamine oxidase inhibitors and sumatriptan tablet is contraindicated.

Sumatriptan tablet must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

### 4.4 Special warnings and precautions for use

Sumatriptan should only be used where there is a clear diagnosis of migraine.

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

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

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

Sumatriptan should not be given to patients with risk factors for ischaemic heart disease without prior cardiovascular evaluation (See Section 4.3 contraindications). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs).

If concomitant treatment with sumatriptan and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised.

Sumatriptan should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of drugs, e.g. impaired hepatic or renal function. A 50mg dose should be considered in patients with hepatic impairment.

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 tablet in these patients.

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

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
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 monoamine oxidase inhibitors (MAOIs), ergotamine and derivatives of ergotamine. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contra-indicated (See also section 4.3).

There are limited data on an interaction with preparations containing ergotamine 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 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-HT1 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-HT1 receptor agonist.

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 Pregnancy and lactation

Post-marketing data from the use of sumatriptan tablet 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 tablet in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on pre and postnatal development. However, embryofoetal viability might be affected in the rabbit (see section 5.3). Administration of sumatriptan tablet should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

It has been demonstrated that following subcutaneous administration, sumatriptan is excreted into breast milk. Infant exposure can be minimised by
avoiding breast feeding for 12 hours after treatment during which time any breast milk expressed should be discarded.

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 events are listed below by system organ class and frequency [4]. 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: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoesthesia.

Vascular Disorders
Common: Transient increases in blood pressure arising soon after treatment. Flushing.

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.

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).

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). 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, nystagmus, scotoma

**Eye disorders**
Very rare: 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**
Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see Contraindications, Warnings and Precautions).

**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

There have been some reports of overdosage with Sumatriptan Tablets. Doses in excess of 400mg orally were not associated with side effects other than those mentioned.

If overdosage occurs, the patient should be monitored for at least ten hours and standard supportive treatment applied as required.

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of Sumatriptan tablet.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: N02CC01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine1 (5HT1D) receptor agonist with no effect on other 5HT receptor (5-HT2-5-HT7) subtypes. The vascular 5-HT1D receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and / or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man.

In addition, evidence from animal studies suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions (cranial vasoconstriction and inhibition of trigeminal nerve activity) may contribute to the anti-migraine action of sumatriptan in humans.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sumatriptan 100mg Film-coated Tablets:

- Lactose monohydrate
- Microcrystalline cellulose (Avicel PH 101)
- Microcrystalline cellulose (Avicel PH 200)
- Pregelatinized starch (Starch 1500)
- Croscarmellose Sodium
- Magnesium Stearate
- Hypromellose
Titanium Dioxide  
Purified Talc  
Macrogol 6000  
Purified water

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 condition.

6.5 Nature and contents of container

Alu / Alu blister, pack sizes of 6, 12 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

BRISTOL LABORATORIES LIMITED  
Unit 3, Canalside, Northbridge Road  
Berkhamsted, Herts, HP4 1EG  
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)

17907/0217

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/03/2009

10 DATE OF REVISION OF THE TEXT

24/03/2009
UKPAR Bristol Laboratories Ltd, Sumatriptan 50mg and 100mg Film-coated Tablets

35