Safeguarding public health

MHRA

Public Assessment Report

SUMATRIPTAN 50 MG TABLETS
SUMATRIPTAN 100 MG TABLETS

PL 00289/0586-9

(SUMATRIPTAN SUCCINATE)

Medicines and Healthcare products Regulatory Agency

SUMATRIPTAN TABLETS

(sumatriptan succinate) PL 00289/0586-9

UKPAR

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SUMATRIPTAN 50 AND 100 MG TABLETS

(SUMATRIPTAN SUCCINATE)

PL 00289/0586-9

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted TEVA UK Limited Marketing Authorisations (licence) for medicinal products Sumatriptan 50 and 100 mg Tablets (PL 00289/0586-9). Sumatriptan is an analgesic indicated for the acute relief of migraine attacks, with or without aura. This is a prescription only medicine [POM].

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.

The clinical data presented to the MHRA, before licensing, demonstrated that sumatriptan tablets are bioequivalent to the reference products, Imigran 50 and 100 mg Tablets (Glaxo Wellcome UK Limited; PL 10949/0222 and 0031). A Marketing authorisation was approved for this product in the UK in 1992, however Imigran 100 mg tablets were first authorised in Europe in the Netherlands on 16th May 1991.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using sumatriptan tablets outweigh the risks; hence a Marketing Authorisation has been granted.

SUMATRIPTAN 50 AND 100 MG TABLETS

(SUMATRIPTAN SUCCINATE)

PL 00289/0586-9

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 50 and 100 mg tablets (PL 00289/0586-9) to TEVA UK Limited on 6th July 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC as amended, claiming essential similarity to Imigran Tablets (Glaxo Wellcome UK) first approved in The Netherlands on 16th May 1991.

The product contains the active ingredient sumatriptan. Sumatriptan is an analgesic: 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.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 00289/0586-9
PROPRIETARY NAME: Sumatriptan 50 and 100 mg Tablets
ACTIVE(S): Sumatriptan succinate
COMPANY NAME: TEVA UK Limited
E.C. ARTICLE: Article 10.1 [formerly Article 10.1(a)(iii) of Directive 2001/83/EC]
LEGAL STATUS: POM

1. INTRODUCTION

1.1 Legal Basis

These are national, abridged applications submitted under Article 10.1 and claiming essential similarity to Imigran Tablets, marketed by Glaxo Wellcome UK. The date of first approval in The Netherlands is stated as 16th May 1991.

1.2 Use

Sumatriptan is an analgesic: Sumatriptan Tablets are 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.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Sumatriptan 50 and 100 mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain Sumatriptan equivalent to 50 and 100 mg. The tablets are packed into transparent or white opaque PVC/PVdC aluminium blisters. Blister packs of 2, 3, 4, 6, 12, 18, 24, 30 and 50 tablets will be marketed. The proposed shelf-life (24 months) with no special storage conditions is consistent with the details registered for the cross-reference products.

2.3 Legal status

These products will be subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG.

The Qualified Person responsible for pharmacovigilance is stated and their CV is included.

2.5 TSE

The suppliers of excipients have confirmed compliance with BSE/TSE guidelines.

DRUG SUBSTANCE

One source of active ingredient is approved to supply the finished product manufacturer. The active substance from this source is the subject of a Drug Master Files (DMF). Full assessment of the DMF has been performed.

A copy of the current DMF edition of the applicant's part has been provided in the CTD format. A letter of access is provided**.**

A satisfactory drug substance specification is included in the DMF.

The finished product manufacturer has also provided a drug substance specification. Certificates of Analysis (CoAs) for batches of the drug substance tested on receipt have been provided.

Analytical Procedures

Analytical procedures are described.

Validation of Analytical Procedures

Satisfactory validation data are provided for the analytical procedures.

Batch Analysis

Results of industrial scale batches of sumatriptan are within specification.

Reference standards

Satisfactory primary and working reference standards are identified.

Stability

Batches stored under ICH real time conditions show compliance with set limits during the approved retest period.

DOSAGE FORM

Composition

The composition is satisfactory and tabulated below.

Name of constituents	Function	Reference to Standards
Active constitutent		
Sumatriptan	Active	Ph. Eur
Other constitutents		
Croscarmellose sodium		Ph. Eur
Lactose monohydrate		Ph. Eur
Cellulose microcrystalline		Ph. Eur
Colloidal anhydrous silica		Ph. Eur
Magnesium stearate	Lubricant	Ph. Eur
Hypromellose E464 Titanium Dioxide E171 Macrogol 3000 Glycerol triacetate Red iron oxide E172 Yellow iron oxide E172 Black iron oxide E172	Coat	Ph. Eur Ph. Eur Ph. Eur Ph. Eur HSE HSE HSE

The two strengths of film-coated tablets are direct scale up or scale down versions of each other and differentiated by tablet size, colour and markings.

PHARMACEUTICAL DEVELOPMENT

Drug Substance

Sumatriptan is slightly soluble in water and freely soluble in methanol. It does not show polymorphism.

Excipients

The excipients chosen for the sumatriptan tablets are the similar to the commercially available Imigran Tablets, marketed by Glaxo Wellcome UK. The formulation is tablets, comprising of excipients that comply with Ph. Eur except the iron oxide red, black and yellow that complies with in house specifications. The function and concentration of the excipients used is standard and accepted.

Pharmacokinetic studies

Satisfactory CoAs are provided for the biobatches.

Container Closure System

The tablets are packed into transparent or white opaque PVC/PVdC aluminium blisters. Blister packs of 2, 3, 4, 6, 12, 18, 24, 30 and 50 tablets are approved for marketing.

Data are provided for the primary packaging to show compliance with EU food safety requirements

Compatibility
Stated 'not relevant' but can be inferred from the product stability data, and accepted.

MANUFACTURE

GMP Statement and Manufacturing Chain
The sites of batch release are Teva UK Limited and Pharmachemie BV (The Netherlands). The sites of manufacture and assembly are also stated. A satisfactory copy of the GMP certificate issued by the relevant Government Agency has been provided. In accordance with GMP arrangements within the EEA, this is acceptable.

Description of the Manufacturing Process
A satisfactory formula and description of manufacture are provided.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place.

The analytical methods and limits are the same as those used in finished product testing and comply with current guidelines and accepted. The tablets are blister packed with satisfactory in-process controls.

In-process batch data for validation batches are satisfactory. The validation results demonstrate homogeneity of blends and consistent manufacture.

The validation protocol provided is considered adequate for the purpose.

Control of Excipients
The list of excipients, complying with Ph. Eur. requirements, is given under "Composition of the medicinal product" above. Iron oxide red, black and yellow comply with in house specifications.

Satisfactory Certificates of Analysis have been provided for each excipient and are accepted. The relevant compendial methodology is used in testing.

Specifications
A satisfactory finished product specification is provided.

Analytical Procedures
Satisfactory validation data are provided.

Batch data
Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed. Dissolution data including standard deviations and profiles are reported.

Characterisation of Impurities
This is satisfactory.

Reference Samples
A batch of sumatriptan succinate characterised against the compendial (EPCRS) Reference standard was used as the working reference standard in testing.

Container Closure System
Satisfactory details of supplier specification, product construction, standards and compliance statements are provided. In-house specifications giving details of tests performed on receipt are provided.

Standard Storage Conditions
Based on stability data at normal, intermediate and accelerated conditions a shelf life is proposed. The data support a product shelf-life of 24 months. This medicinal product does not require any special storage conditions.
The samples provided for stability studies are representative of the product to be marketed in the proposed pack.

The programme is ongoing. The stability programme is satisfactory as the applicant has agreed to place the first commercial batches on stability.

The results of the stability studies support the proposed shelf life.

Bioanalytical Methods and Validation
Satisfactory methodology and validation data are provided.

Quality Overall Summary
This is satisfactory.

Essential Similarity
The following data support essential similarity:

a) Acceptable choice of test and reference products
b) Acceptable bioequivalence between test and reference product.
c) Comparative dissolution profiles are provided for test and reference product.
d) The impurity profile of the test product is comparable with that of the reference product and considered satisfactory.
e) The active substances conform to Ph. Eur. requirements and comply with relevant principles in ICH guidelines.

PRODUCT PARTICULARS

Product Brand Name
This is considered satisfactory.

Summary of Product Characteristics
Satisfactory SPC provided.

Patient Information Leaflet
Satisfactory coloured mock-ups are provided**.** The applicant has until 1st July 2008 to amend the order in which the information appears in the leaflet and provide user testing data (both parts of Article 59, Directive 2004/27/EC must be complied with at the same time).

Labelling
Satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA) form

This is satisfactory.

ADDITIONAL DATA REQUIREMENTS

Satisfactory.

CONCLUSION

A product licence may be granted for this product.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

These comprise a complex and three standard national abridged applications for sumatriptan tablets under EC Article 10,1 [formerly10.1(a)(iii), first paragraph] of the Directive 2001/83/EC.

Essential similarity is claimed to the reference products Imigran 50 & 100 mg Tablets (PLs 10949/0222 &0031, Glaxo Wellcome UK Ltd). Imigran 100 mg tablets were first authorised in Europe in the Netherlands on 16 May 1991.

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

2. INDICATIONS

The UK approved indication in the SPC is:

> "Sumatriptan tablets are 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"

3. DOSE & DOSE SCHEDULE

The UK approved dosage regimen in the SPC is:

Adults

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

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

The recommended dose of oral sumatriptan is a single 50 mg tablet. Some patients may require 100 mg. If the patient has responded to the first dose but the symptoms recur a second dose may be given in the next 24 hours provided that there is a minimum interval of two hours between the two doses and no more than 300 mg is taken in any 24 hour period.

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

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

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

Elderly (Over 65)
Experience of the use of sumatriptan in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

4. TOXICOLOGY

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

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.
The kinetic profile of sumatriptan is known as it has already been authorised and in clinical use for many years. The applicant has investigated the bioequivalence of the product compared with the reference product (Imigran Tablets, Glaxo Wellcome).

5.1 BIOEQUIVALENCE

A bioequivalence study was carried out and the test and reference products shown to be bioequivalent (within the customary 90% confidence intervals) for the appropriate pharmacokinetic criteria. Although the study was conducted using 100 mg tablets, the case is adequately made to extend the satisfactory comparison to include the 50 mg strength.

Study 02198 – B0202: A randomised, 2-way crossover bioequivalence study of Sumatriptan 100 mg Tablets and Imigran 100 mg Tablets

Objective: To compare the rate and extent of absorption of a test sumatriptan versus a reference product (Imigran) sumatriptan, administered as 1 x 100 mg tablet in healthy adult subjects under fasting conditions.

Subjects: 26 healthy adults between 19 and 40 yrs old.

Test: Sumatriptan succinate 100 mg tablets.

Reference: Sumatriptan succinate [Imigran] 100 mg tablets.

Duration of treatment: Single oral dose was administered under fasting conditions in each study period. Treatment phases were separated by a washout of seven days [NB elimination half life is around two hours].

Blood sampling: prior to drug administration and at 0.166, 0.333, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 hrs post dose in each period.

Criteria: primary were AUC_{0-t} and C_{max}; other parameters were AUC_{0-inf}, T_{max}, K_{el}, $T_{1/2el}$ and residual area. Descriptive safety data were recorded.

Statistical methods:

Pharmacokinetics

Parametric ANOVA on AUC_{0-t}, $C_{max,}$ AUC_{0-inf}, K_{el}, $T_{1/2el;}$ geometric confidence intervals for AUC_{0-t} and $C_{max,}$ $AUC_{0-inf,}$ and non-parametric test (Wilcoxon Signed-Rank test) for T_{max} with derivation of non-parametric 90% confidence interval.

Covariates in the ANOVA model: Sequence, subject (sequence), period and treatment.

Ln-transformed parameters: AUC_{0-t}, $C_{max,}$ $AUC_{0-inf.}$

Criteria for Bioequivalence:

The 90% geometric confidence interval of the ratio (A/B) of least-squares means from ANOVA of the Ln transformed AUC_{0-t} and C_{max} should be between 80.00 to 125.00%.

Results:

Comparative Pharmacokinetics:

	Sumatriptan test	**Imigran reference**	**Test/Ref Ratio**	**Test/Ref (90% CI) #**
AUC0-t (ng/ml h) mean (SD)	190.87 (50.08)	186.84 (34.65)	100.80%	94.98% to 106.99%
AUC0-inf (ng/ml h) mean (SD)	199.71 (51.49)	195.38 (35.36)	100.95%	95.34% to 106.89%
Cmax (ng/ml) mean (SD)	46.70 (13.04)	45.85 (11.32)	101.11%	92.42% to 110.62%
Tmax (h) median (range)	1.33 (2.38)	1.33 (1.39)		
T1/2el (h) median (range)	2.38 (0.42)	2.48 (0.420		

 # for T_{max} medians and interquartile ranges are presented instead of means and SD.

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.

As the two strengths of the proposed product are dose proportional qualitatively and quantitatively then the results of 100 mg tablet can be considered applicable to the 50 mg 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 Clinical Overview has been provided in CTD Module 2.5.
A Clinical Summary has not been provided in CTD Module 2.7.
Information about the Clinical Expert is provided in CTD Module 1.4.3.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The SPCs are considered satisfactory and are consistent with the SPCs for the reference product.

10. PATIENT INFORMATION LEAFLET

The PILs are considered satisfactory and are consistent with the PILs for the reference product.

11. LABELLING

The labelling is considered satisfactory.

12. DISCUSSION

The clinical use of sumatriptan is well established in the indications proposed. The bioequivalence of the tablets have been shown. No new clinical efficacy and safety data has been submitted and none are required.

13. CONCLUSIONS

Overall, there is no clinical objection to the grant of marketing authorisations for these applications. No new or unexpected safety concerns arise from these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

Sumatriptan is a well known drug and has been used as an analgesic for many years. Bioequivalence has been demonstrated between the applicant's sumatriptan tablets and the innovator product, 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 cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with sumatriptan is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

SUMATRIPTAN 50 AND 100 MG TABLETS

(SUMATRIPTAN SUCCINATE)

PL 00289/0586-9

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 19th March 2003.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 14th September 2005.
3	Following assessment of the application the MHRA requested further information on 15th September 2005.
4	The applicant responded to the MHRA's requests, providing further information on 4th October 2005.
5	The application was determined on 6th July 2006

SUMATRIPTAN 50 AND 100 MG TABLETS

(SUMATRIPTAN SUCCINATE)

PL 00289/0586-9

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SUMATRIPTAN 50 MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL(S) 00289/0586 & 0588

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of sumatriptan (as sumatriptan succinate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong shaped cores debossed “5” and “0” on one side and scoreline on each side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

It is advisable that sumatriptan 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 of oral sumatriptan is a single 50 mg tablet. Some patients may require 100 mg. If the patient has responded to the first dose but the symptoms recur a second dose may be given in the next 24 hours provided that there is a minimum interval of two hours between the two doses and no more than 300 mg is taken in any 24 hour period.

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

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

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

Elderly (Over 65 years of age)
Experience of the use of sumatriptan in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

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 signs consistent with ischaemic heart disease.

Sumatriptan should not be administered to patients with a history of cerebovascular accident (CVA) or transient ischaemic attack (TIA).

Sumatriptan should not be administered to patients with severe hepatic impairment.

The use of sumatriptan in patients with moderate and severe hypertension and mild uncontrolled hypertension is contraindicated.

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (See Section 4.5.).

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.

Sumatriptan injection 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 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 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. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is limited but caution should be exercised before using sumatriptan in these patients

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

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.

Lactose
Sumatriptan Tablets contain lactose and should therefore not be used in patients with rare genetic disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. Sumatriptan 50 mg Tablets contain 71.1 mg of lactose monohydrate per tablet.

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 (see also Contraindications). The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contra-indicated. (see also contraindications).

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

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

Rarely, an interaction may occur between sumatriptan and SSRI's (see Section 4.4.).

4.6 Pregnancy and lactation

Use during pregnancy
Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they

do not point to an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.
Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and postnatal development. However, embryofoetal viability might be affected in the rabbit (see section 5.3).

Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the fœtus.

Use during breast-feeding
It has been demonstrated that following subcutaneous administration sumatriptan is secreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment.

4.7 Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with sumatriptan.
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: Tingling, dizziness, drowsiness.

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

Gastrointestinal
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).

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 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

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: antimigraine preparations: selective 5-HT_1, receptor agonists

ATC Code N02CC01

Sumatriptan has been demonstrated to be a specific and selective 5-Hydroxytryptamine$_1$ ($5HT_{1D}$) receptor agonist with no effect on other 5HT receptor (5-HT_2-5-HT_7) subtypes. The vascular 5-HT_{1D} receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man.

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

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

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

Although the recommended dose of oral sumatriptan is 50 mg, migraine attacks vary in severity both within and between patients. Doses of 25 – 100 mg have shown greater efficacy than placebo in clinical trials, but 25 mg is statistically significantly less effective than 50 and l00 mg.

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 100 mg dose, the maximum plasma concentration is 54 ng/ml. Mean absolute oral bioavailability is 14 % partly due to presystemic metabolism and partly due to incomplete absorption. The 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 1160 ml/min and the mean renal plasma clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80 % of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5HT_1$ or $5HT_2$ activity. Minor metabolites have not been identified. The pharmacokinetics of oral sumatriptan do not appear to be significantly affected by migraine attacks.

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

5.3 Preclinical safety data

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

In a rat ferfility 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

Core
Lactose monohydrate
Croscarmellose sodium
Cellulose, microcrystalline
Silica colloidal anhydrous
Magensium stearate

Coating – Opadry peach
Hypromellose E464
Titanium dioxide E171
Lactose monohydrate
Macrogol
Glycerol triacetate
Iron oxide red E172
Iron oxide yellow E172
Iron oxide black E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent or white opaque PVC/PVdC aluminium blisters.
Blister packs of 2, 3, 4, 6, 12,18, 24, 30 and 50 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Ltd
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0586 and PL 00289/0588

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2006

10 DATE OF REVISION OF THE TEXT

September 2006

SUMATRIPTAN 100 MG TABLETS
(sumatriptan succinate)
PL(s) 00289/0587 & 0589

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of sumatriptan (as sumatriptan succinate).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong shaped cores debossed “100” on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

The recommended dose of oral sumatriptan is a single 50 mg tablet. Some patients may require 100 mg. If the patient has responded to the first dose but the symptoms recur a second dose may be given in the next 24 hours provided that there is a minimum interval of two hours between the two doses and no more than 300 mg is taken in any 24 hour period.

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

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

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

Elderly (Over 65)
Experience of the use of sumatriptan in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

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 signs consistent with ischaemic heart disease.

Sumatriptan should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Sumatriptan should not be administered to patients with severe hepatic impairment.

The use of sumatriptan in patients with moderate and severe hypertension and mild uncontrolled hypertension is contraindicated.

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated. (See Section 4.5.)

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.

Sumatriptan Injection 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 opthalmoplegic 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 with 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 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 should be administered with caution in 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. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is limited but caution should be exercised before using sumatriptan in these patients

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

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.

Lactose
Sumatriptan Tablets contain lactose and should therefore not be used in patients with rare genetic disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. Sumatriptan 100 mg Tablets contain 142.2 mg of lactose monohydrate per tablet.

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 also contraindications).

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

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

Rarely, an interaction may occur between sumatriptan and SSRI's (see Section 4.4.).

4.6 Pregnancy and lactation

Use during pregnancy
Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not point to an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.
Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and postnatal development. However, embryofoetal viability might be affected in the rabbit (see section 5.3).

Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the fœtus.

Use during breast-feeding
It has been demonstrated that following subcutaneous administration sumatriptan is secreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment.

4.7 Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with sumatriptan. 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: Tingling, dizziness, drowsiness.

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

Gastrointestinal
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).
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.).

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: antimigraine preparations: selective 5-HT_1, receptor agonists

ATC Code N02CC01

Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine$_1$, (5HT $_{1D}$) receptor agonist with no effect on other 5HT receptor (5-HT_2 – 5-HT_7) subtypes. The vascular 5-HT_{1D} receptor is found predominantly in cranial blood vessels, and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extra cranial and intracranial tissues, such as the meninges and dilatation 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 30 minutes following a 100 mg oral dose.

Although the recommended dose of oral sumatriptan is 50 mg, migraine attacks vary in severity both within and between patients. Doses of 25 - 100 mg have shown greater efficacy than placebo in clinical trials, but 25 mg is statistically significant1y less effective than 50 and 100 mg.
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 100 mg dose the maximum plasma concentration is 54 ng/ml. Mean absolute oral bioavailability is 14% partly due to presystemic metabolism and partly due to incomplete absorption. The 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 1160 ml/min and the mean renal plasma clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5HT_1$ or $5HT_2$ activity. Minor metabolites have not been identified. The pharmacokinetics of oral sumatriptan do not appear to he 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

Core
Lactose monohydrate
Croscarmellose sodium
Cellulose, microcrystalline
Silica colloidal anhydrous
Magensium stearate

Coating – Opadry white
Hypromellose E464
Titanium dioxide E171
Lactose monohydrate
Macrogol
Glycerol triacetate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent or white opaque PVC/PVdC aluminium blisters.
Blister packs of 2, 3, 4, 6, 12, 18, 30 and 50 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Ltd
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0587 and PL 00289/0589

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2006

10 DATE OF REVISION OF THE TEXT

15/05/2006

SUMATRIPTAN 50 & 100 MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 00289/0586-9

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sumatriptan 50 and 100 mg Tablets

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- Ask your doctor or pharmacist if you have any further questions.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- Tell your doctor or pharmacist if any of the side effects get serious, or if you notice any side effects not listed in this leaflet.

IN THIS LEAFLET:

1. What Sumatriptan is and what it is used for

- Sumatriptan belongs to a group of drugs called $5HT_1$ receptor agonists, which are used to relieve migraine symptoms.
- Your medicine is used to treat migraine attacks.

2. Before you take Sumatriptan tablets

Do NOT take Sumatriptan tablets if you:

- Are allergic (hypersensitive) to sumatriptan or any of the other ingredients of this medicine
- Are taking any other medicines for migraine which contain ergotamine or ergotamine derivatives, e.g. ergotamine tartrate or methysergide
- Are taking or have taken in the last two weeks, any medicine known as a monoamine oxidase inhibitor (MAOI), which is used to treat depression, e.g. moclobemide or phenelzine
- Have had a stroke or a TIA (transient ischaemic attack – a mild and transient form of stroke)
- Have severe liver disease
- Have any of the following medical conditions: heart disease such as heart failure, angina or have suffered a heart attack
- Have high blood pressure (unless recommended to take Sumatriptan tablets by your doctor).

Talk to your doctor or pharmacist if you:

- Have a higher than average risk of suffering from heart disease e.g. a family history of heart disease, diabetes, high blood cholesterol, you are a regular cigarette smoker or are very

* Only marketed pack sizes will be included in the printed version of the PIL

overweight, especially if you are a man over 40 years old or a woman who has been through the menopause
- Have liver or kidney disease, as you may require a slightly reduced dose. You should follow your doctor's instructions
- Are sensitive to sulphonamides (used to treat infections), e.g. sulfadiazine, as you may also be sensitive to this medicine
- Have a history of seizures
- Have a liver function test as sumatriptan may influence the result.

Check with your doctor if you are taking any of the following:

- Products that contain the herbal remedy St John's wort (*Hypericum perforatum*)
- Lithium or selective serotonin re-uptake inhibitors (SSRIs) e.g. fluoxetine and paroxetine, which are used to treat depression.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding:

- Do not take Sumatriptan tablets without first telling your doctor if you are pregnant, likely to become pregnant, or are breast-feeding.

Driving and using machines:

- Suffering from a migraine and taking Sumatriptan tablets can both cause drowsiness. If you are affected, do not drive or operate machinery.

Important information about some of the ingredients of Sumatriptan Tablets
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Sumatriptan tablets

Always use Sumatriptan exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The tablets should be swallowed whole with a drink of water.

The usual dosage instructions are given below:

Adults

Take one 50 mg tablet at the first sign of a migraine attack (although the tablet will still be effective if taken at a later stage). Some patients may need to take 100 mg, so please follow your doctor's instructions.

If the first dose does not make your migraine better, do not take any more tablets because it is unlikely that a second dose will work. Sumatriptan tablets can however be used for your next migraine attack.

If, after your first dose, your migraine goes away but then returns, you may take another dose, provided it is at least **two hour**s since you took the first dose.

Do **not** take more than six 50 mg tablets or three 100 mg tablets in any 24-hour period, that is 300 mg in total.

Children (under 18 years of age)

Not recommended.

Elderly (over 65 years of age)

Not recommended.

If you take more Sumatriptan tablets than you should

If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

After starting to take your tablets

If the Sumatriptan tablets do not ease your migraine, then you may take other 'painkillers' e.g. aspirin or paracetemol. Do not take medicines which contain ergotamine or ergotamine derivatives until at least 6 hours since your last dose of Sumatriptan.

4. Possible side effects

Like all medicines, Sumatriptan tablets can have side effects, although not everybody gets them.

If the following happens, stop taking Sumatriptan tablets and tell your doctor immediately or go to the casualty department at your nearest hospital:

An allergic reaction causing
- Difficulty in breathing and swelling of the lips, face and neck
- A skin rash such as red spots or nettle rash.

This is a serious but very rare side effect. You may need urgent medical attention or hospitalisation.

If you experience severe chest pain after taking Sumatriptan, **tell your doctor immediately** and do not take any more tablets. Your doctor will decide if you should stop using them. There have been extremely rare cases of such chest pains being caused by a heart attack.

The following side effects have been reported at the approximate frequencies shown:

Common (affecting fewer than one person in 10 but more than one person in 100)
- A feeling of warmth, heaviness, pressure, tightness or sometimes pain in different parts of the body including the chest or throat (although sometimes intense usually only lasts a few minutes)
- Nausea and vomiting
- Tingling, drowsiness or tiredness

- Dizziness, flushing
- Increase in blood pressure

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):
- Feelings of weakness or fatigue.

Very rare (affecting fewer than one person in 10,000):
- Neck stiffness
- Inflammation of the colon, resulting in abdominal pressure and bloody diarrhoea
- Low blood pressure which make you feel light-headed or faint.
- Poor circulation, coldness in the fingers and toes, which is known as Raynaud's phenomenon.
- Changes in the heart rate (either faster or slower)
- Palpitations
- Fits or seizures (usually in people with a history of epilepsy)
- Tremors
- Abnormal muscle rigidity
- Involuntary movement of the eye
- Reduced vision, flickering and rolling of the eyes, double vision and very rarely loss of sight. However, problems with vision may occur as a result of the migraine
- Minor disturbances in liver function tests.

Tell your doctor or pharmacist if any of the side effects get serious, or if you notice any side effects not listed in this leaflet.

5. How to store Sumatriptan tablets

Keep Sumatriptan tablets out of the reach and sight of children. Do not transfer to another container. Do not use Sumatriptan tablets after the expiry date shown on the outer packaging.

Do not dispose of medicines in household waste or wastewater. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

Ingredients:
- The active ingredient is sumatriptan (as succinate)
- The other ingredients are:
  - Tablet core: lactose, croscarmellose sodium, colloidal anhydrous silica, microcrystalline cellulose and magnesium stearate
  - Tablet coating: hypromellose, titanium dioxide (E171), macrogol and triacetin. The 50 mg tablets also contain iron oxides red, yellow and black (E172).

Contents of the Pack:
- The name of your medicine is Sumatriptan 50 & 100 mg Tablets.
- Each film-coated tablet contains either 50 mg or 100 mg of sumatriptan (as succinate).
- The product is available in pack sizes* of 2, 3, 4, 6, 12, 18, 30 and 50 tablets. The 50 mg product is also available in pack sizes of 24 tablets.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder and company responsible for manufacture is TEVA UK Limited, Eastbourne, BN22 9AG.

Distributed by TEVA UK, Leeds, LS27 0JG.

The leaflet was last revised: May 2006

SUMATRIPTAN 50 MG TABLETS
(SUMATRIPTAN SUCCINATE)
PL 00289/0586 & 0588

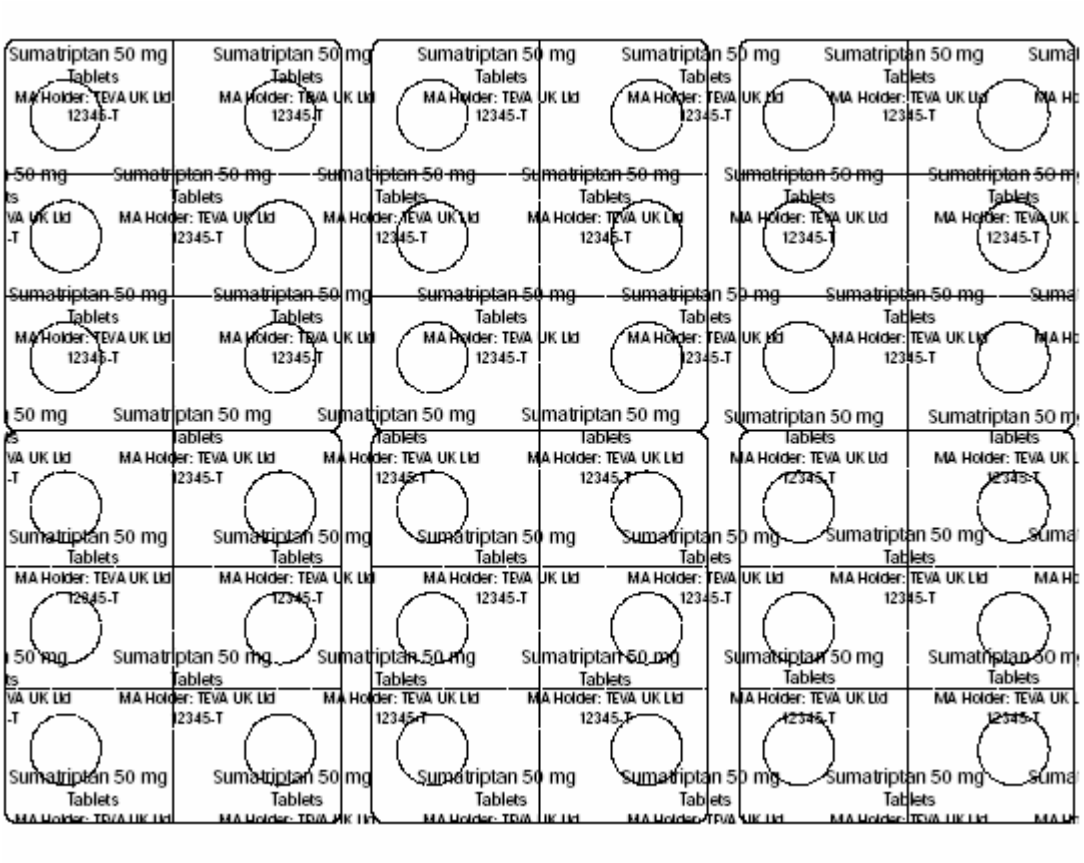
CARTON LABEL

SUMATRIPTAN 100 MG TABLETS (SUMATRIPTAN SUCCINATE)

CARTON LABEL

SUMATRIPTAN 50 MG TABLETS
(SUMATRIPTAN SUCCINATE)

FOIL LABEL



SUMATRIPTAN 100 MG TABLETS
(SUMATRIPTAN SUCCINATE)

FOIL LABEL