SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

UKPAR

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SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

LAY SUMMARY

The MHRA today granted J & P Pharma UK Ltd Marketing Authorisations (licenses) for the medicinal products Sumatriptan 50mg and 100mg Tablets (PL 21621/0001-4 and 0006-7). These are prescription only medicines (POM) for the acute relief of migraine attacks, with or without aura. Sumatriptan tablets should only be used where there is a clear diagnosis of migraine.

Sumatriptan 50mg and 100mg Tablets contain the active ingredient sumatriptan as the succinate. Sumatriptan is a vascular 5-HT_1 receptor agonist which acts to relieve migraine headache.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Sumatriptan 50mg and 100mg Tablets outweighs the risks, hence Marketing Authorisations have been granted.

SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Sumatriptan 50mg and 100mg Tablets to J & P Pharma UK Ltd (PL 21621/0001-4 0006-7) on 8th of May 2006. The products are prescription only medicines.

These applications comprise of a complex and standard abridged National Marketing Application for Sumatriptan 50 & 100 mg tablets made under EC Article 10.1 (a) (iii), first paragraph. The proposed legal status is Prescription Only Medicine.

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

Sumatriptan is a vascular 5-HT_1 receptor agonist which acts to relieve migraine headache.

These applications for Sumatriptan 50mg and 100mg Tablets were submitted at the same time. A bioequivalence study was carried out and the test and reference products were shown to be bioequivalent for the appropriate pharmacokinetic criteria. Although the bioequivalence study was conducted using 100mg tablets, the case is adequately made to extend the satisfactory comparison to include the 50 mg strength

PHARMACEUTICAL ASSESSMENT

Active substance

Sumatriptan succinate is a white powder, freely soluble in water with a molecular formula of $C_{18}H_{27}N_3O_6S$ and molecular weight of 413.5. This active is the subject of a Ph.Eur monograph.

Specifications are provided for the starting materials along with test methods.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Certificates of analysis in favour of the excipient specifications have also been provided.

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised.

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

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

Appropriate stability data have been generated. The data support a shelf life of 2 years and there are no special storage conditions.

Other ingredients

Other ingredients consist of Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, purified talc, and colloidal anhydrous silica in the tablet. The film coat consists of Hypromellose, macrogol, purified talc, titanium dioxide (E171), Lake with cochineal red (E124 – mixture of aluminium hydroxide and 1-(4-sulpho-1-naphthylazo)-2-naphthol-6, 8-disulphonic acid)), triethyl citrate.

All excipients used are Ph.Eur grade material apart from lake with cochineal red E124. This complies with E number 124 and is routinely tested. Named impurities are also controlled in line with the Ph.Eur.

Product development and finished product

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The function of each excipient is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

In vitro dissolution profiles have been generated for the product. The results were satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

The finished product specifications proposed for both release and shelf life are acceptable and provide an assurance of the quality and consistency of the finished product. The analytical methods used have been suitably validated. Batch analysis data has demonstrated compliance with the proposed release specification.

Stability of the product

All results from stability studies were within the specified limits. These data support a shelf-life of 2 years for the product packaged in Polyamide/Alu/ PVC/ Alu blister packs in a cardboard carton. The product has no special instructions for storage.

Bioequivalence/bioavailability

A bioequivalence study has been performed between reference product and test product Sumatriptan 100mg tablets manufactured at the proposed manufacturing site. Bioequivalence was demonstrated for the 100mg Tablets and justification given for application to the 50mg tablets. Satisfactory Certificates of Analysis have been provided for the test and reference batches.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

CONCLUSION

It is recommended that Marketing Authorisations are granted for these applications.

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. BACKGROUND

These applications comprise of a complex and standard abridged National Marketing Application for Sumatriptan 50 & 100 mg tablets made under EC Article 10.1 (a) (iii), first paragraph. The proposed legal status is Prescription Only Medicine.

The reference medicinal products are Imigran 50 & 100 mg Tablets (PL 10949/0222 & 0231, GlaxoSmithKline, UK - granted in 1991).

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

Sumatriptan is a selective 5-HT_1 receptor agonist used in the treatment of migraine.

2. INDICATIONS

The proposed indication section in the SPC is:

"Therapeutic indications

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

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

Medical Assessor's Comment

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

3. DOSE & DOSE SCHEDULE

The proposed dosage recommendations are:

The tablets should be swallowed whole with water.

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.

Adults only:

Sumatriptan tablets are 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 an attack of migraine but it is equally effective at whatever stage of the attack it is administered.

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

If a patient does not respond to the first dose of Sumatriptan tablets, a second should not be taken for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Patients who respond initially but whose migraine returns may take further doses in the next 24 hours provided that there is a minimum interval of two hours between doses. A maximum dose of 300 mg in any 24 hour period should not be exceeded.

Children (under 18 years):

The safety and effectiveness of sumatriptan tablets in children and adolescents under 18 years has not been established.

Elderly (more than 65 years):

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

Medical Assessor's Comment: The dose and dose schedule is satisfactory and is in line with the reference product.

4. TOXICOLOGY

No new data are provided or needed. The pharmaco-toxicological expert's CV has extensive and appropriate experience and qualifications. The SPC sections on pregnancy and lactation (4.6) and preclinical safety data (5.3) are consistent with those of the reference product.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacodynamics

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

Sumatriptan is a specific and selective agonist of vascular 5-hydroxytryptamine$_1$ receptor.

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

In animals, sumatriptan causes selective vasoconstriction in the carotid arterial circulation that supplies blood to extracranial and intracranial tissues, such as the meninges. The dilatations of these vessels and/or oedema formation in and around these vessels have been thought to be the underlying mechanism of migraine in humans.

The results of animal studies show that sumatriptan also inhibits the activity of the trigeminal nerve. Both actions (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine inhibiting effect of sumatriptan in humans.

The clinical response begins 10 – 15 minutes after a subcutaneous injection of 6mg, 15 minutes after intranasal administration of 20mg and about 30 minutes after an oral dose of 100mg or a rectal dose of 25mg.

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

5.2 Pharmacokinetics

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

Binding to plasma proteins is low (14 – 21%) and the mean distribution volume is 170 litres. The mean total clearance is approximately 1160ml/min and the mean renal clearance is approximately 260ml/min. The non-renal

clearance accounts for about 80% of the total clearance, which indicates that sumatriptan is primarily eliminated by metabolism. The main metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine, where it is present as free acid and glucuronide conjugate. It possesses no known $5HT_1$ or $5HT_2$ activity. Minor metabolites have not been identified. Migraine attacks do not seem to have a significant effect on the pharmacokinetics of orally administered sumatriptan.

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

5.3 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 100mg tablets, the case is adequately made to extend the satisfactory comparison to include the 50 mg strength.

6. EFFICACY

No new clinical efficacy data have been submitted with this application. None are required. There is adequate experience for 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 submitted. The clinical expert's qualifications are appropriate as are the pharmaco-toxicological expert's.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The summary of product characteristics is satisfactory. The text of the summary of product characteristics is essentially the same as that of the reference products.

10. PATIENT INFORMATION LEAFLET

This is satisfactory.

11. LABELLING

This is satisfactory.

12. RECOMMENDATION

Medical Assessor:
A marketing authorisation may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Sumatriptan 50 mg 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.

PRECLINICAL

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

EFFICACY

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

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

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 product and the reference product are interchangeable. 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 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 11th August 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on the 20th October 2004
3	Following assessment of the application the MHRA requested further information on the 11/01/2006
4	The applicant responded to the MHRA's requests, providing further information on 08/03/2006
5	The application was determined on the 8th May 2006

SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sumatriptan (as the succinate).

Also contains: lactose monohydrate, cochineal red (E124). For full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Sumatriptan 50mg tablets are light pink, film-coated, oblong, biconvex tablets, with a scoreline.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

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

4.2 Posology and Method of Administration

The tablets should be swallowed whole with water.

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.

Adults only:

Sumatriptan tablets are 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 an attack of migraine but it is equally effective at whatever stage of the attack it is administered.

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

If a patient does not respond to the first dose of Sumatriptan tablets, a second should not be taken for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Patients who respond initially but whose migraine returns may take further doses in the next 24 hours provided that there is a minimum interval of two hours between doses. A maximum dose of 300 mg in any 24 hour period should not be exceeded.

Children (under 18 years):

The safety and effectiveness of sumatriptan tablets in children and adolescents under 18 years has not been established.

Elderly (more than 65 years):

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

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Sumatriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or sign 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 - interactions).

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.

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

4.4 Special Warnings and Special 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 ischemic 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 – Undesirable Effects*). Where such symptoms are thought to indicate ischemic 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 ischemic 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 weakness, hyper-reflexia, and in-coordination 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.

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is

limited, however, caution should be exercised before using sumatriptan in these patients.

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

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5. Interactions with other medicinal products and other forms of interaction

Studies in healthy subjects show that Sumatriptan does not interact with propranolol, 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 contra-indicated. (see also section 4.3 - 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.

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contra-indicated (see section 4.3 - Contraindications). Rarely, an interaction may occur between sumatriptan and SSRI’s (see section 4.4 - Special Warnings and special Precautions for Use).

4.6. Pregnancy and lactation

Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not point to an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and postnatal development. However, embryofoetal viability might be affected in the rabbit (see section 5.3 – Preclinical Safety Data).

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

It has been demonstrated that following subcutaneous administration sumatriptan is secreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 24 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

General

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat; pain, sensations of tingling, heat, heaviness, pressure or tightness. The following symptoms are mild to moderate in intensity and transient: flushing, dizziness and feelings of weakness.

Fatigue and drowsiness have been reported.

Cardiovascular

Hypotension, bradycardia, tachycardia, palpitations.

Transient increases in blood pressure arising soon after treatment have been recorded. In extremely rare cases, serious coronary events have been reported which have included cardiac arrhythmias, ischaemic ECG changes, coronary artery vasospasm or myocardial infarction. (see section 4.3 - Contraindications, and section 4.4 - Precautions and Warnings).

There have also been rare reports of Raynaud's phenomenon and ischaemic colitis.

Gastrointestinal

Nausea and vomiting occurred in some patients but the relationship to Sumatriptan is not clear.

CNS

There have been rare reports of seizures following use of sumatriptan. 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.

Eye Disorders

Patients treated with Imigran rarely exhibit visual disorders like flickering and diplopia.
Additionally, cases of nystagmus, scotoma and reduced vision have been observed.
Very rarely loss of vision has occurred, which is usually transient. However, visual disorders may also occur during a migraine attack itself.

Hypersensitivity/skin

Hypersensitivity reactions ranging from cutaneous hypersensitivity to, in rare cases, anaphylaxis.

Laboratory values

Minor disturbances in liver function tests have occasionally been observed.

4.9. Overdose

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 Imigran

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics: Selective 5-HT1 receptor agonists.
ATC code: N02C C01

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.

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 100 mg.

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 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 100mg 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

Tablet:

Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, purified talc, colloidal anhydrous silica.

Film coat:

Hypromellose, macrogol, purified talc, titanium dioxide (E171), Lake with cochineal red (E124 – mixture of aluminium hydroxide and 1-(4-sulpho-1-naphthylazo)-2-naphthol-6,8-disulphonic acid)), triethyl citrate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

No special storage conditions

6.5. Nature and contents of container

Polyamide/Alu/PVC/Alu blister packs in a cardboard carton with Patient Information Leaflet. Pack sizes may include 1, 2, 4, 6, 12 or 18 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

J & P Pharma UK Ltd
Dorest House
Regent Park
297 Kingston Road
Leatherhead
Surrey
KT22 7PL
UK

8. MARKETING AUTHORISATION NUMBER

PL 21621/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/05/2006

10 DATE OF REVISION OF THE TEXT

08/05/2006

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg sumatriptan (as the succinate).
Also contains: lactose monohydrate.

For full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Sumatriptan 100 mg tablets are white, film-coated, oblong, biconvex tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

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

4.2. Posology and method of administration

The tablets should be swallowed whole with water.

Adults only
Sumatriptan tablets are 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 50mg tablet. Some patients may require 100mg.

If the patient has responded to the first dose of Sumatriptan tablets, a second should not be taken for the same attack. Sumatriptan tablets may be taken for subsequent attacks.

Patients who respond initially but whose migraine returns may take further doses in the next 24 hours provided that there is a minimum interval of two

hours between doses. A maximum dose of 300mg in any 24 hour period should not be exceeded.

Children (Under 18 years)

The safety and effectiveness of Sumatriptan tablets in children and adolescents under 18 years has not been established

Elderly (Over 65 years of age)

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

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Sumatriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or sign 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 - interactions).

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.

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

4.4. Special warnings and precautions for use

Imigran 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 – Undesirable 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 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.

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of Sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is limited, however, caution should be exercised before using sumatriptan in these patients.

Undesirable effects may be more common during concomitant use of tripans and herbal preparations containing St Johns wort *(Hypericum perforatum).*

4.5. Interactions with other medicinal products and other forms of interaction

Studies in healthy subjects show that Sumatriptan does not interact with propranolol, 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 contra-indicated. (see also section 4.3 - 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.

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contra-indicated (see section 4.3 - Contraindications). Rarely, an interaction may occur between sumatriptan and SSRI's (see section 4.4 - Special Warnings and special Precautions for Use).

4.6. Pregnancy and lactation

Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not point to an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and postnatal development. However, embryofoetal viability might be affected in the rabbit (see section 5.3 – Preclinical Safety Data).

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

It has been demonstrated that following subcutaneous administration sumatriptan is secreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 24 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

General

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat; pain, sensations of tingling, heat, heaviness, pressure or tightness. The following symptoms are

mild to moderate in intensity and transient: flushing, dizziness and feelings of weakness.

Fatigue and drowsiness have been reported.

Cardiovascular

Hypotension, bradycardia, tachycardia, palpitations.

Transient increases in blood pressure arising soon after treatment have been recorded. In extremely rare cases, serious coronary events have been reported which have included cardiac arrhythmias, ischaemic ECG changes, coronary artery vasospasm or myocardial infarction. (see section 4.3 - Contraindications, and section 4.4 - Precautions and Warnings).

There have also been rare reports of Raynaud's phenomenon and ischaemic colitis.

Gastrointestinal

Nausea and vomiting occurred in some patients but the relationship to Sumatriptan is not clear.

CNS

There have been rare reports of seizures following use of sumatriptan. 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.

Eye Disorders

Patients treated with Imigran rarely exhibit visual disorders like flickering and diplopia.
Additionally, cases of nystagmus, scotoma and reduced vision have been observed.
Very rarely loss of vision has occurred, which is usually transient. However, visual disorders may also occur during a migraine attack itself.

Hypersensitivity/skin

Hypersensitivity reactions ranging from cutaneous hypersensitivity to, in rare cases, anaphylaxis.

Laboratory values

Minor disturbances in liver function tests have occasionally been observed.

4.9. Overdose

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 Imigran

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics: Selective 5-HT_1 receptor agonists.

ATC code: N02C C01

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

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

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.

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.

5.2. Pharmacokinetic properties

Following oral administration, Sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After 100mg dose, the maximum plasma concentration is 54ng/ml. Mean absolute oral bioavailability

is 14% partly due to presystemic metabolism and partly due to incomplete absorption. The elimination phase half-life is approximately 2 hours, although there is an indication of a longer terminal phase. Plasma protein binding is low (14-21%), mean volume of distribution is 170 litres. Mean total plasma clearance is approximately 11 60ml/min and the mean renal plasma clearance is approximately 260ml/min. Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of Sumatriptan is mainly excreted in the urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5HT_1$ or $5HT_2$ activity. Minor metabolites have not been identified. The pharmacokinetics of oral Sumatriptan do not appear to be significantly affected by migraine attacks.

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

5.3. Preclinical safety data

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

In a rat fertility study oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man after a 100mg 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

Tablet:

Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, purified talc, colloidal anhydrous silica.

Film coat:

Hypromellose, macrogol, purified talc, titanium dioxide (E171), triethyl citrate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

No special storage conditions

6.5. Nature and contents of container

Polyamide/Alu/PVC/Alu blister packs in a cardboard carton with Patient Information Leaflet. Pack sizes may include 1, 2, 3, 4, 6, 12, 18 or 20 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

J & P Pharma UK Ltd
Dorest House
Regent Park
297 Kingston Road
Leatherhead
Surrey
KT22 7PL
UK

8. MARKETING AUTHORISATION NUMBER

PL 21621/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/05/2006

10 DATE OF REVISION OF THE TEXT

08/05/2006

SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

INFORMATION LEAFLET
SUMATRIPTAN 50 mg, 100 mg
USMM-1951-020
DRAWING – VERSION 3
AVERSE

Patient information leaflet

polpharma

Sumatriptan

(sumatriptan succinate)
50 mg 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*
- *If you have further questions, please ask your doctor or pharmacist*
- *This medicine has been prescribed for you personally. Do not give it to anyone else. It may harm them, even if their symptoms are the same as yours.*

IN THIS LEAFLET

1. *What Sumatriptan tablets are and what are they used for*
2. *Before you take Sumatriptan tablets*
3. *How to take Sumatriptan tablets*
4. *Possible side effects*
5. *Storing Sumatriptan tablets*

YOUR MEDICINE

Sumatriptan is available in two strengths containing either 50 mg or 100 mg of the active ingredient sumatriptan (as the succinate). The other ingredients are lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, talc, colloidal anhydrous silica, hypromellose, macrogol 6000, titanium dioxide (E171), cochineal red (E124 - 50 mg tablets only) and triethyl citrate.

The 50 mg film coated tablets are light pink in colour, oblong, biconvex, tablets with a scoreline.

The 100 mg film coated tablets are white in colour, oblong, biconvex tablets.

Sumatriptan 50 mg and 100 mg tablets are available in blister packs of 1, 2, 3, 4, 6, 12, 18 or 20 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder: *J&P Pharma UK. LTD., Dorset House, Regent Park, 297 Kingston Road, Leatherhead, Surrey, KT22 7PL, United Kingdom*

Manufacturer: *Z.F. Polpharma SA, ul. Pelplinska 19, 83-200 Starogard Gdanski, Poland*

WHAT SUMATRIPTAN IS AND WHAT THIS MEDICINE IS USED FOR

Your medicine comes as a tablet containing sumatriptan. Sumatriptan tablets are 5HT$_1$ antagonists. Sumatriptan is an antimigraine medicine used to treat migraine attacks. A migraine causes attacks of headache, sometimes with sickness or other symptoms e.g. some people become sensitive to light or noise.

Sumatriptan should not be used where migraine has not been diagnosed.

BEFORE YOU TAKE SUMATRIPTAN

Do not take this medicine and tell your doctor if:

- *you are allergic to sumatriptan or any other ingredients in this tablet, especially E124 in the 50 mg tablet, which may cause allergic reactions.*
- *you have an intolerance to some sugars as this medicine contains lactose*
- *you have heart problems such as heart disease or angina*
- *you have had a heart attack or stroke in the past*
- *you have severe liver problems*
- *your blood pressure is not controlled or you are being treated for high blood pressure (hypertension)*
- *you are already taking medicines containing ergotamine or methysergide (to treat migraine)*
- *you are already taking medicine to treat mental illness e.g. an MAOI (monoamine oxidase inhibitor), lithium or an antidepressant*
- *you have stopped MAOI treatment in the last 2 weeks*
- *you are pregnant, or likely to become pregnant, or are breast-feeding.*

You must tell your doctor before taking Sumatriptan if:

- *you have liver or kidney problems or,*
- *you have hardened arteries or are at risk from blood clots*
- *you are taking any sulphonamides.*

Pregnancy and breast feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Sumatriptan may make you feel drowsy. Do not drive or operate machinery if you feel drowsy.

HOW TO TAKE SUMATRIPTAN

- *Take Sumatriptan as soon as possible after the start of the migraine attack*
- *Swallow the tablet whole with a glass of water.*

Adults

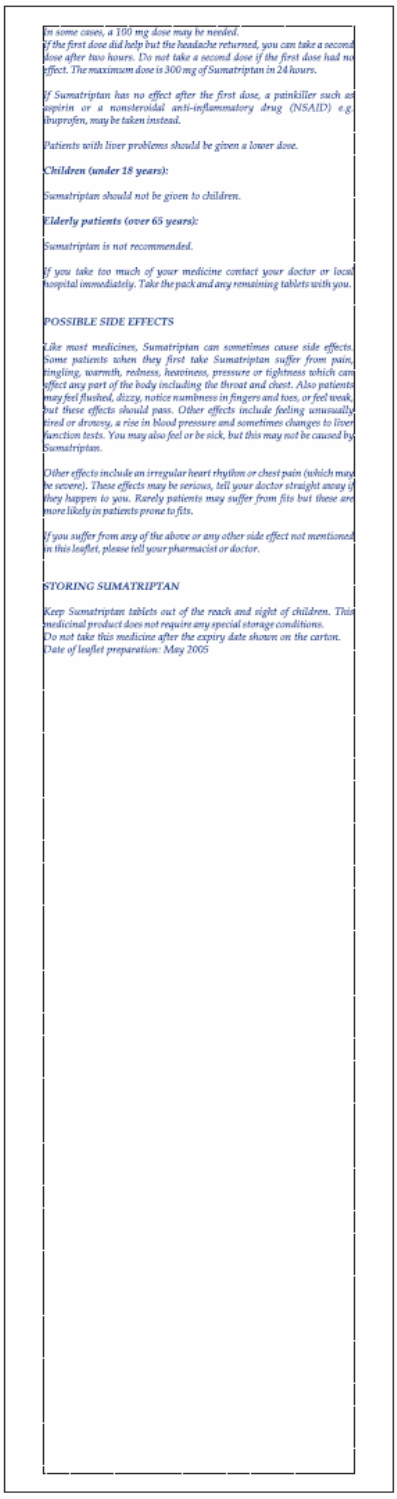
Take one 50 mg tablet.

Pantone 2747 C

SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

INFORMATION LEAFLET
SUMATRIPTAN 50 mg, 100 mg
USMM-1951-020
DRAWING – VERSION 3
REVERSE



In some cases, a 100 mg dose may be needed.
If the first dose did help but the headache returned, you can take a second dose after two hours. Do not take a second dose if the first dose had no effect. The maximum dose is 300 mg of Sumatriptan in 24 hours.

If Sumatriptan has no effect after the first dose, a painkiller such as aspirin or a nonsteroidal anti-inflammatory drug (NSAID) e.g. ibuprofen, may be taken instead.

Patients with liver problems should be given a lower dose.

Children (under 18 years):

Sumatriptan should not be given to children.

Elderly patients (over 65 years):

Sumatriptan is not recommended.

If you take too much of your medicine contact your doctor or local hospital immediately. Take the pack and any remaining tablets with you.

POSSIBLE SIDE EFFECTS

Like most medicines, Sumatriptan can sometimes cause side effects. Some patients when they first take Sumatriptan suffer from pain, tingling, warmth, redness, heaviness, pressure or tightness which can affect any part of the body including the throat and chest. Also patients may feel flushed, dizzy, notice numbness in fingers and toes, or feel weak, but these effects should pass. Other effects include feeling unusually tired or drowsy, a rise in blood pressure and sometimes changes to liver function tests. You may also feel or be sick, but this may not be caused by Sumatriptan.

Other effects include an irregular heart rhythm or chest pain (which may be severe). These effects may be serious, tell your doctor straight away if they happen to you. Rarely patients may suffer from fits but these are more likely in patients prone to fits.

If you suffer from any of the above or any other side effect not mentioned in this leaflet, please tell your pharmacist or doctor.

STORING SUMATRIPTAN

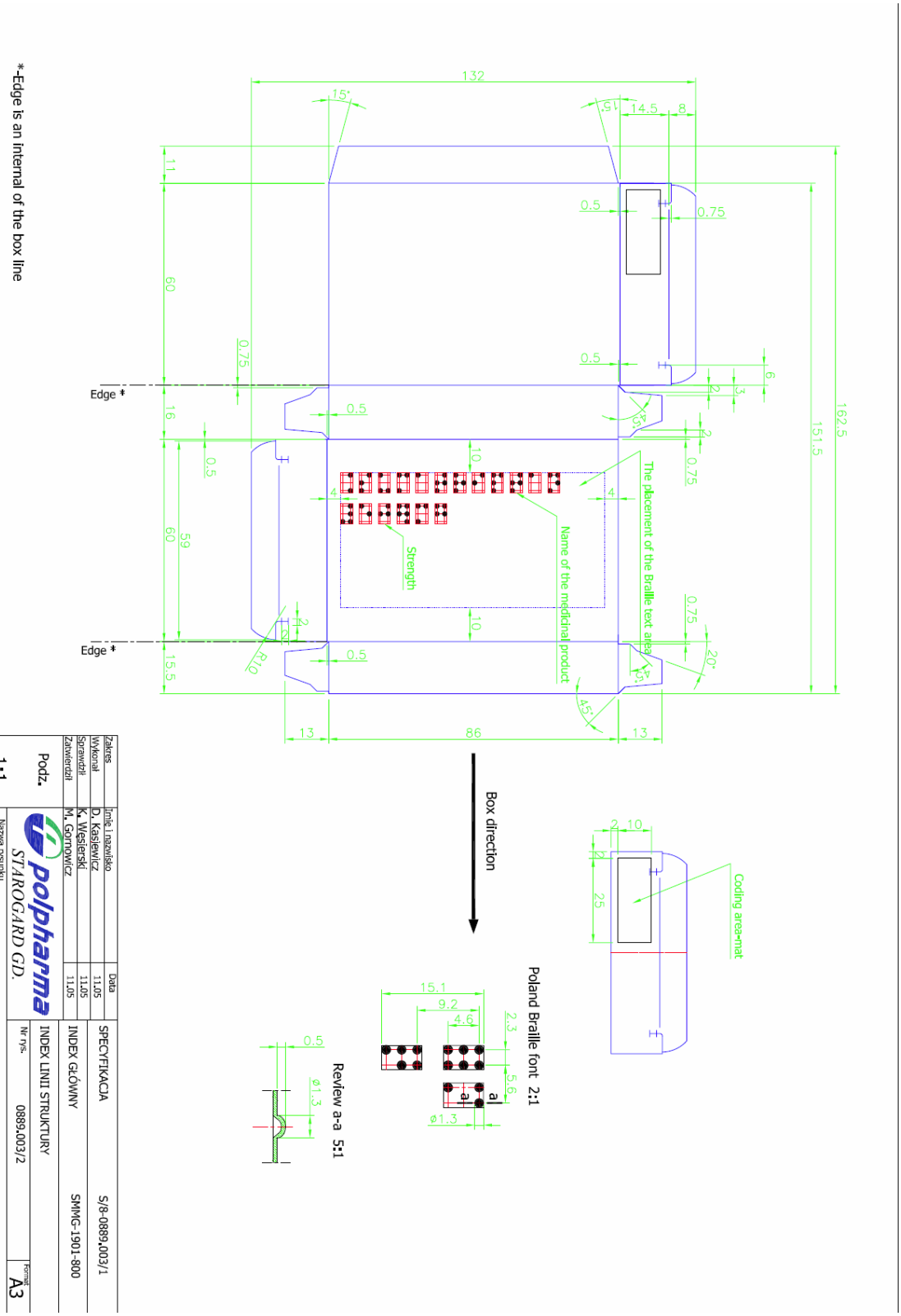
Keep Sumatriptan tablets out of the reach and sight of children. This medicinal product does not require any special storage conditions.
Do not take this medicine after the expiry date shown on the carton.
Date of leaflet preparation: May 2005

SUMATRIPTAN 50MG TABLETS
PL 21621/0001 and 0003 and 0006

CARTON BOX WITH OVERPRINT
SUMATRIPTAN 50 mg x 2 film-coated tablets
DRAWING - KSMM-1753-020/10

Logo: Pantone 3275 C
Pantone 444 C

ATTENTION! Colouring on the basis of KTK
Pantone 2747 C
Pantone Cool Gray 5
Pantone 361 C OVERPRINT
Pantone 375 C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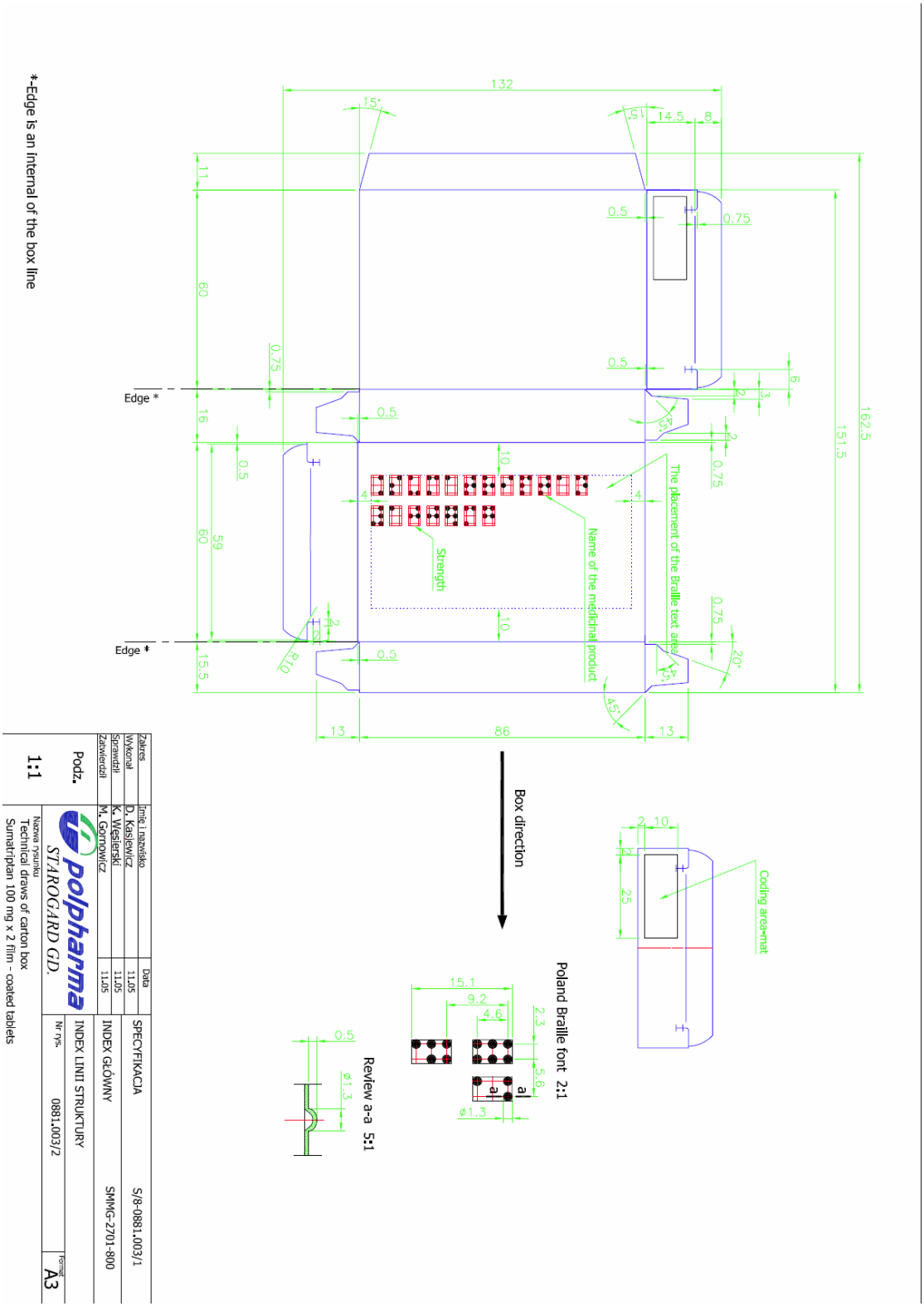
SUMATRIPTAN 100MG TABLETS
PL 21621/0002 and 0004 and 0007

CARTON BOX WITH OVERPRINT
SUMATRIPTAN 100 mg x 2 film-coated tablets
DRAWING - KSMM-1745-020/10

Logo: Pantone 3275 C
Pantone 444 C

ATTENTION! Colouring on the basis of KTK
Pantone 2747 C
Pantone Cool Gray 5
Pantone 361 C OVERPRINT
Pantone 375 C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Technical draws of carton box
Sumatriptan 100 mg x 2 film - coated tablets