SUMATRIPTAN 50MG TABLETS
PL 00530/0762

SUMATRIPTAN 100MG TABLETS
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UKPAR

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LAY SUMMARY

The MHRA today granted Norton Healthcare Ltd (Trading as IVAX Pharmaceuticals UK) Marketing Authorisations (licenses) for the medicinal products Sumatriptan 50mg and 100mg Tablets (PL 00530/0762-3). 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
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Sumatriptan 50mg and 100mg Tablets to Norton Healthcare Ltd (Trading as IVAX Pharmaceuticals UK) PL 00530/0762-3 on 15th of May 2006. The products are prescription only medicines.

These national abridged applications (1 complex, 1 standard) for Sumatriptan tablets are made under EC Article 10.1(a) (iii) of the Directive 2001/83/EC.

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 with the storage condition of “Do not store above 30°C”.

Other ingredients

Other ingredients consist of Lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, magnesium stearate (E572), red iron oxide (E172).
All excipients used are Ph Eur grade material apart from red iron oxide which is controlled to USP/NF.
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 clear colourless PVC/PVDC Aluminium foil blister strips in a cardboard carton. The product has instructions for storage “Do not store above 30°C”.

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).

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

The SPC is essentially identical to the UK innovator SPC.

3. DOSE & DOSE SCHEDULE

The proposed dosage recommendations are:

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

Sumatriptan should be taken as early as possible when the migraine pain has appeared. Sumatriptan is equally effective administered at whatever stage of the attack.

Administration

The tablet(s) should be swallowed whole with water

Adults

The recommended dose for adults is a single 50 mg tablet. For some patients 100 mg may be necessary.

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

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.

If the patient does not respond to the first dose of sumatriptan, another dose should not be taken for the same attack. Sumatriptan may be used for subsequent attacks.

If symptoms have disappeared with the first dose but they recur, 1 or 2 additional doses can be taken during the next 24 hours, provided that there is a minimum interval of two hours between the doses and not more then 300 mg is taken during this period.

The recommended dose should not be exceeded.

For the different dosage regimens sumatriptan is available in the strength of 50 and 100 mg.

Hepatic insufficiency

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

Children and adolescents (under 18 years)

Sumatriptan Tablet is not recommended for use in children below age 18 due to a lack of data on safety and/or efficacy (see section 5.2)

Elderly patients

Experience of the use of sumatriptan in patients over 65 years is limited. The kinetics in elderly patients have not been sufficiently studied. The use of sumatriptan in patients over 65 years is not recommended until further clinical data are available.

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

5. CLINICAL PHARMACOLOGY

5.1 Pharmacodynamics

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

ATC code: N02CC01

Sumatriptan is a specific and selective agonist of vascular 5-hydroxytryptamine$_1$ receptor with no effect on other 5HT receptor sub-types. This type of receptors have mainly been found in cranial blood vessels. In animals, sumatriptan causes selectively vasoconstriction in the carotid arterial circulation that supplies blood to extracranial and intracranial tissues, such as the meninges. The dilatation of these vessels has been thought to be the underlying mechanism of migraine in humans. The results of animal studies show that sumatriptan also inhibits the activity of the trigeminal nerve. Both actions (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine inhibiting effect of sumatriptan in humans.

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.

The clinical response begins around 30 minutes after an oral dose of 100 mg.

5.2 Pharmacokinetics

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 100 mg is 54 ng/ml. The mean absolute bioavailability after oral administration is 14%, partly due to presystemic

metabolism and partly due to incomplete absorption. The elimination half-life is approximately 2 hours, although there is an indication of a longer terminal phase.

Binding to plasma proteins is low (14 - 21%) and the mean distribution volume is 170 litres. The mean total clearance is approximately 1160 ml/min and the mean renal clearance is approximately 260 ml/min. The non-renal clearance accounts for about 80% of the total clearance, which indicates that sumatriptan is primarily eliminated by metabolism. The metabolic elimination of sumatriptan is mediated by monoamine oxidase A. The main metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine, 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.

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

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 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 when the SPC and other product literature have been finalised and approved.

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.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 21st December 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on the 26th January 2005.
3	Following assessment of the application the MHRA requested further information on the 14/06/2005 and on the 05/10/2005
4	The applicant responded to the MHRA's requests, providing further information on 26/09/2005 and on the 05/05/2006
5	The application was determined on the 15/05/2006

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SUMATRIPTAN 100MG TABLETS
PL 00530/0763

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sumatriptan base as the succinate salt.

For a full list of excipients, see section 6.1. Also contains lactose.

3. PHARMACEUTICAL FORM

Tablet

Light pink coloured, round, biconvex tablets engraved with ‘SUM 50’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Sumatriptan is indicated for the acute treatment 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

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

Sumatriptan should be taken as early as possible when the migraine pain has appeared. Sumatriptan is equally effective administered at whatever stage of the attack.

Administration

The tablet(s) should be swallowed whole with water

Adults

The recommended dose for adults is a single 50 mg tablet. For some patients 100 mg may be necessary.

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

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.

If the patient does not respond to the first dose of sumatriptan, another dose should not be taken for the same attack. Sumatriptan may be used for subsequent attacks.

If symptoms have disappeared with the first dose but they recur, 1 or 2 additional doses can be taken during the next 24 hours, provided that there is a minimum interval of two hours between the doses and not more then 300 mg is taken during this period.

The recommended dose should not be exceeded.

For the different dosage regimens sumatriptan is available in the strength of 50 and 100 mg.

Hepatic insufficiency

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

Children and adolescents (under 18 years)

Sumatriptan Tablet is not recommended for use in children below age 18 due to a lack of data on safety and/or efficacy (see section 5.2)

Elderly patients

Experience of the use of sumatriptan in patients over 65 years is limited. The kinetics in elderly patients have not been sufficiently studied. The use of sumatriptan in patients over 65 years is not recommended until further clinical data are available.

4.3. Contraindications

Hypersensitivity to sumatriptan or to any of the excipients or to sulphonamides (see section 4.4).

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

Sumatriptan must 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.

Concurrent administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see section 4.5).

Concurrent administration of sumatriptan with reversible (e.g. moclobemide) or irreversible (e.g. selegiline) monoamine oxidase inhibitors (MAOIs) is contraindicated.

Furthermore, sumatriptan must not be used within two weeks of discontinuation of therapy with irreversible 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.

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

It should be taken into account that migraine patients may have an increased risk to be affected by certain cerebrovascular disorders (e.g. CVA, TIA). 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.

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, including those patients who are heavy smokers or users of nicotine substitution therapies without prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

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 the absorption, metabolism or excretion of the medicinal product, 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 the 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).

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

The recommended dose of sumatriptan should not be exceeded.

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

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

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

There are limited data on an interaction with ergotamine-containing preparations. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated (see section 4.3).

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations is not known. This will also depend on the doses and type of ergotamine-containing products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine-containing preparations before administering sumatriptan. Conversely it is advised to wait at least six hours following use of sumatriptan before administering an ergotamine-containing product (see section 4.3).

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see section 4.3). Rarely an interaction may occur between sumatriptan and SSRIs.

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

4.6. Pregnancy and lactation

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

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

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

4.7. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

Drowsiness may occur as a result of migraine or its treatment with sumatriptan. This may influence the ability to drive and to operate machinery.

4.8. Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10), common (> 1/100, < 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.

***Gastrointestina*l disorders**
Common: Nausea and vomiting occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition.

Musculoskeletal, connective tissue and bone disorders
Common: Sensations of heaviness (usually transient and may be intense and can affect any part of the body including the chest and throat).

General disorders and administration site conditions
Common: Pain, sensations of heat, pressure or tightness (these events are usually transient and may be intense and can affect any part of the body including the chest and throat).

Uncommon: Feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).

Investigations

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

Post-marketing data

Immune system disorders
Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis.

Nervous system disorders
Very rare: Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent.

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 sections 4.3 and 4.4).

Vascular disorders
Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal
Very rare: Ischaemic colitis.

Musculoskeletal, connective tissue and bone disorders
Very rare: Neck stiffness.

4.9. Overdose

Patients have received up to 12 mg of sumatriptan, as a single subcutaneous injection without significant undesirable effects. With subcutaneous doses exceeding 16 mg and oral doses exceeding 400 mg, no other undesirable effects have been observed than those mentioned in section 4.8.

In cases of overdose, the patient should be monitored for at least 10 hours and if necessary standard supportive treatment must be given.

There is no information on the effect of haemodialysis or peritoneal dialysis on plasma sumatriptan concentrations.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

ATC code: N02CC01

Sumatriptan is a specific and selective agonist of vascular 5-hydroxytryptamine$_1$ receptor with no effect on other 5HT receptor sub-types. This type of receptors have mainly been found in cranial blood vessels. In animals, sumatriptan causes selectively vasoconstriction in the carotid arterial circulation that supplies blood to extracranial and intracranial tissues, such as the meninges. The dilatation of these vessels has been thought to be the underlying mechanism of migraine in humans. The results of animal studies show that sumatriptan also inhibits the activity of the trigeminal nerve. Both actions (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine inhibiting effect of sumatriptan in humans.

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.

The clinical response begins around 30 minutes after an oral dose of 100 mg.

5.2. Pharmacokinetic properties

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 100 mg is 54 ng/ml. The mean absolute bioavailability after oral administration is 14%, partly due to presystemic metabolism and partly due to incomplete absorption. The elimination half-life is approximately 2 hours, although there is an indication of a longer terminal phase.

Binding to plasma proteins is low (14 - 21%) and the mean distribution volume is 170 litres. The mean total clearance is approximately 1160 ml/min and the mean renal clearance is approximately 260 ml/min. The non-renal clearance accounts for about 80% of the total clearance, which indicates that sumatriptan is primarily eliminated by metabolism. The metabolic elimination of sumatriptan is mediated by monoamine oxidase A. The main metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine, 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.

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

5.3. Preclinical safety data

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

In a rat fertility study oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man after a 100 mg oral dose were associated with a reduction in the success of insemination.

This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 150 times those in man by the oral route.

In rabbits embryo lethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate

Microcrystalline Cellulose (E460)

Croscarmellose Sodium

Magnesium Stearate (E572)

Iron Oxide Red (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 30ºC

6.5. Nature and contents of container

Clear colourless PVC/PVDC Aluminium foil blister strips in a cardboard carton, containing either 6 or 12 tablets.

6.6 Special precautions for disposal

No special requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd T/A.
IVAX Pharmaceuticals UK
Albert Basin
Royal Docks
London
E16 2QJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00530/0762

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2006

10 DATE OF REVISION OF THE TEXT

15/05/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg sumatriptan base as the succinate salt.

For a full list of excipients, see section 6.1. Also contains lactose.

3. PHARMACEUTICAL FORM

Tablet

White to off-white round, biconvex tablets engraved with ‘SUM 100’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Sumatriptan is indicated for the acute treatment 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

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

Sumatriptan should be taken as early as possible when the migraine pain has appeared. Sumatriptan is equally effective administered at whatever stage of the attack.

Administration

The tablet(s) should be swallowed whole with water.

Adults

The recommended dose for adults is a single 50 mg tablet. For some patients 100 mg may be necessary.

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

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.

If the patient does not respond to the first dose of sumatriptan, another dose should not be taken for the same attack. Sumatriptan may be used for subsequent attacks.

If symptoms have disappeared with the first dose but they recur, 1 or 2 additional doses can be taken during the next 24 hours, provided that there is a minimum interval of two hours between the doses and not more then 300 mg is taken during this period.

The recommended dose should not be exceeded.

For the different dosage regimens sumatriptan is available in the strength of 50 and 100 mg.

Hepatic insufficiency

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

Children and adolescents (under 18 years)

Sumatriptan Tablet is not recommended for use in children below age 18 due to a lack of data on safety and/or efficacy (see section 5.2)

Elderly patients

Experience of the use of sumatriptan in patients over 65 years is limited. The kinetics in elderly patients have not been sufficiently studied. The use of sumatriptan in patients over 65 years is not recommended until further clinical data are available.

4.3. Contraindications

Hypersensitivity to sumatriptan or to any of the excipients or to sulphonamides (see section 4.4).

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

Sumatriptan must 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.

Concurrent administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see section 4.5).

Concurrent administration of sumatriptan with reversible (e.g. moclobemide) or irreversible (e.g. selegiline) monoamine oxidase inhibitors (MAOIs) is contraindicated.

Furthermore, sumatriptan must not be used within two weeks of discontinuation of therapy with irreversible 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.

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

It should be taken into account that migraine patients may have an increased risk to be affected by certain cerebrovascular disorders events (e.g. CVA, TIA).

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.

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, including those patients who are heavy smokers or users of

nicotine substitution therapies without prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

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 the absorption, metabolism or excretion of the medicinal product, 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 the 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).

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

The recommended dose of sumatriptan should not be exceeded.

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

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

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

There are limited data on an interaction with ergotamine-containing preparations. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated (see section 4.3).

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations is not known. This will also depend on the doses and type of ergotamine-containing products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine-containing preparations before administering sumatriptan. Conversely it is advised to wait at least six hours following use of sumatriptan before administering an ergotamine-containing product (see section 4.3).

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see section 4.3). Rarely an interaction may occur between sumatriptan and SSRIs.

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

4.6. Pregnancy and lactation

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

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

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

4.7. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

Drowsiness may occur as a result of migraine or its treatment with sumatriptan. This may influence the ability to drive and to operate machinery.

4.8. Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10), common (> 1/100, < 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.

***Gastrointestina*l disorders**
Common: Nausea and vomiting occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition.

Musculoskeletal, connective tissue and bone disorders
Common: Sensations of heaviness (usually transient and may be intense and can affect any part of the body including the chest and throat).

General disorders and administration site conditions
Common: Pain, sensations of heat, pressure or tightness (these events are usually transient and may be intense and can affect any part of the body including the chest and throat).

Uncommon: Feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).

Investigations

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

Post-marketing data

Immune system disorders
Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis.

Nervous system disorders
Very rare: Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent.

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 sections 4.3 and 4.4).

Vascular disorders
Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal
Very rare: Ischaemic colitis.

Musculoskeletal, connective tissue and bone disorders
Very rare: Neck stiffness.

4.9. Overdose

Patients have received up to 12 mg of sumatriptan, as a single subcutaneous injection without significant undesirable effects. With subcutaneous doses exceeding 16 mg and oral doses exceeding 400 mg, no other undesirable effects have been observed than those mentioned in section 4.8.

In cases of overdose, the patient should be monitored for at least 10 hours and if necessary standard supportive treatment must be given.

There is no information on the effect of haemodialysis or peritoneal dialysis on the plasma sumatriptan concentrations.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

ATC code: N02CC01

Sumatriptan is a specific and selective agonist of vascular 5-hydroxytryptamine$_1$ receptor with no effect on other 5HT receptor sub-types. This type of receptors have mainly been found in cranial blood vessels. In animals, sumatriptan causes selectively vasoconstriction in the carotid arterial circulation that supplies blood to extracranial and intracranial tissues, such as the meninges. The dilatation of in these vessels has been thought to be the underlying mechanism of migraine in humans. The results of animal studies show that sumatriptan also inhibits the activity of the trigeminal nerve. Both actions (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine inhibiting effect of sumatriptan in humans.

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.

The clinical response begins around 30 minutes after an oral dose of 100 mg.

5.2. Pharmacokinetic properties

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 100 mg is 54 ng/ml. The mean absolute bioavailability after oral administration is 14%, partly due to presystemic metabolism and partly due to incomplete absorption. The elimination half-life is approximately 2 hours, although there is an indication of a longer terminal phase.

Binding to plasma proteins is low (14 - 21%) and the mean distribution volume is 170 litres. The mean total clearance is approximately 1160 ml/min and the mean renal clearance is approximately 260 ml/min. The non-renal clearance accounts for about 80% of the total clearance, which indicates that sumatriptan is primarily eliminated by metabolism. The metabolic elimination of sumatriptan is mediated by monoamine oxidase A. The main metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine, 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.

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

5.3. Preclinical safety data

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

In a rat fertility study oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man after a 100 mg oral dose were associated with a reduction in the success of insemination.

This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 150 times those in man by the oral route.

In rabbits embryo lethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate

Microcrystalline Cellulose (E460)

Croscarmellose Sodium

Magnesium Stearate (E572)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 30ºC

6.5. Nature and contents of container

Clear colourless PVC/PVDC Aluminium foil blister strips in a cardboard carton, containing either 6 or 12 tablets.

6.6 Special precautions for disposal

No special requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd T/A
IVAX Pharmaceuticals UK
Albert Basin
Royal Docks
London
E16 2QJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00530/0763

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2006

10. DATE OF REVISION OF THE TEXT

15/05/2006

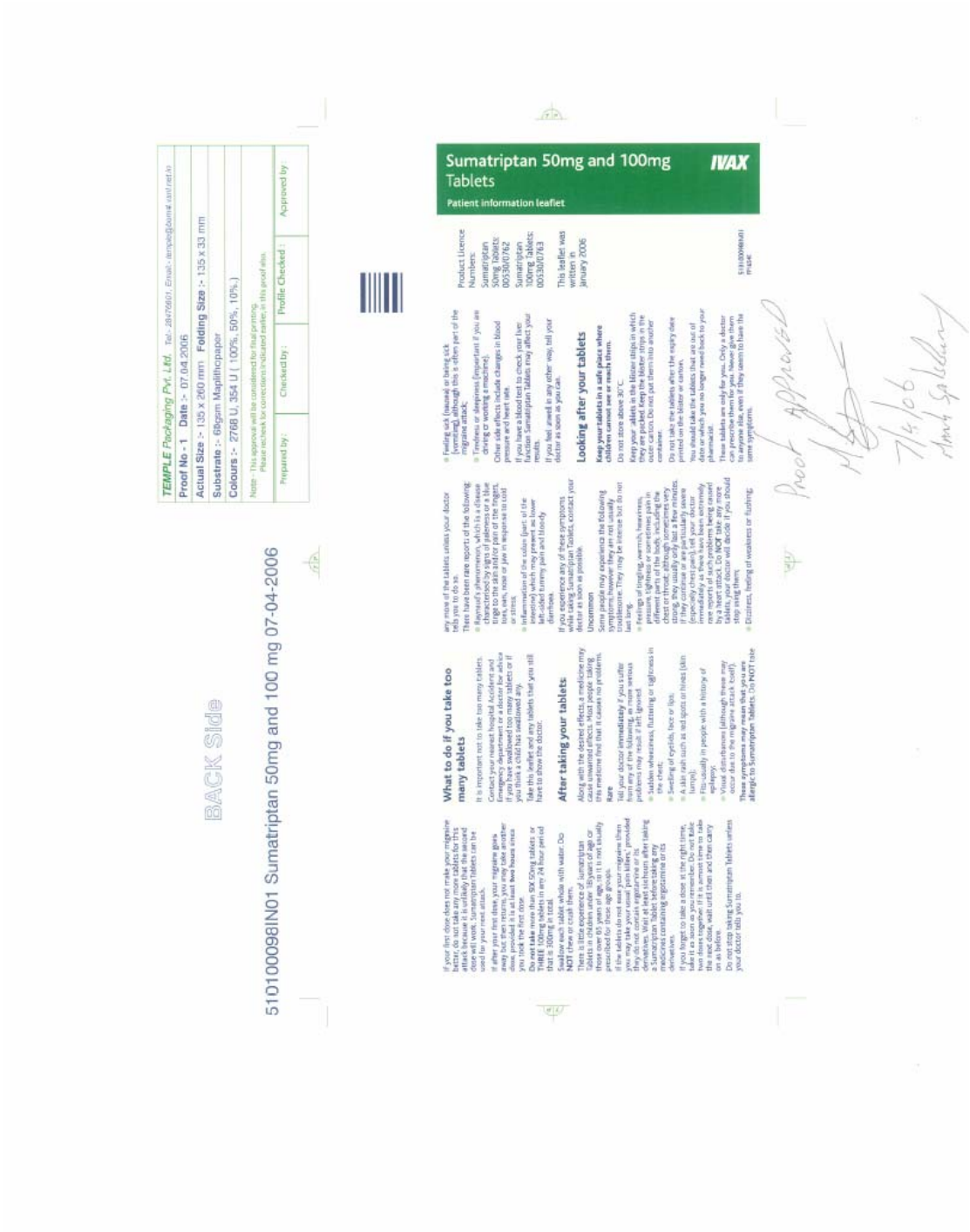
SUMATRIPTAN 50MG TABLETS
PL 00530/0762

SUMATRIPTAN 100MG TABLETS
PL 00530/0763

SUMATRIPTAN 50MG TABLETS
PL 00530/0762

SUMATRIPTAN 100MG TABLETS
PL 00530/0763

Patient Information leaflet



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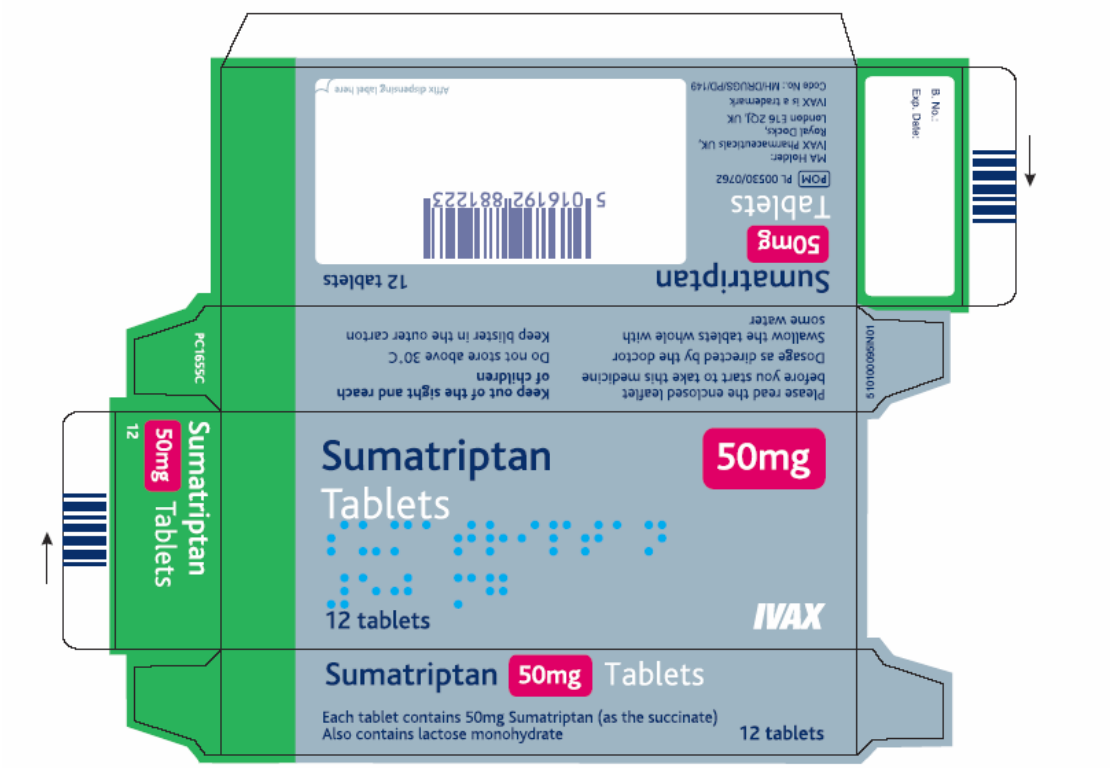

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Graphic Creations

Braille text reads: Sumatriptan (numeral sign) 50mg

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Livery: IUK	Strength: 50MG	REVISER: WA
Last Colour Sep Date: 9/11/04		Artworker's Signature:

Other information:
Braille will be embossed (non-printable colour)

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PMS 2768
PMS 8200

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PMS 2768: 50%-barcode

FONTS USED
Helvetica/ITC Zapf Dingbats (job box)
Bliss various
SD Pharma Braille UK reg.

SOFTWARE USED
Adobe Illustrator 11.0

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SUMATRIPTAN 50MG TABLETS
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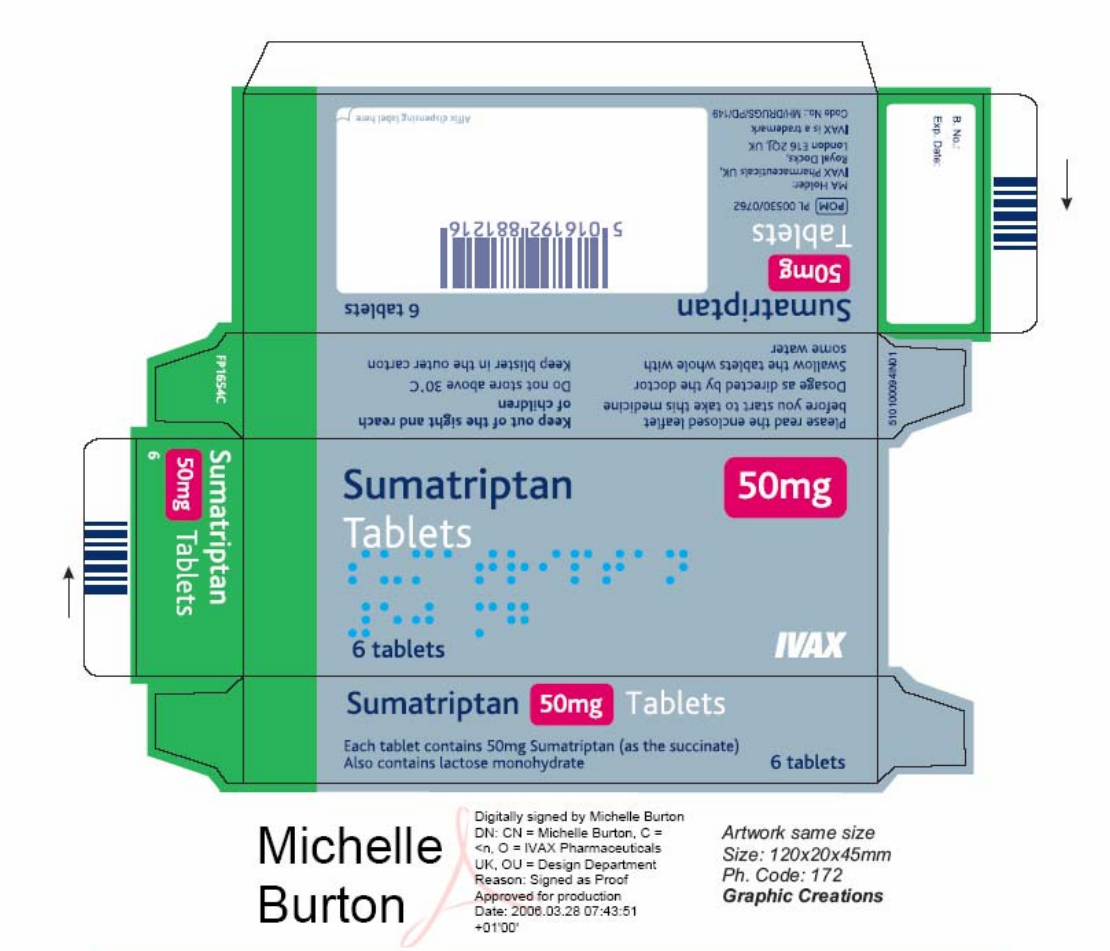

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FONTS USED
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SUMATRIPTAN 50MG TABLETS
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Foil Label

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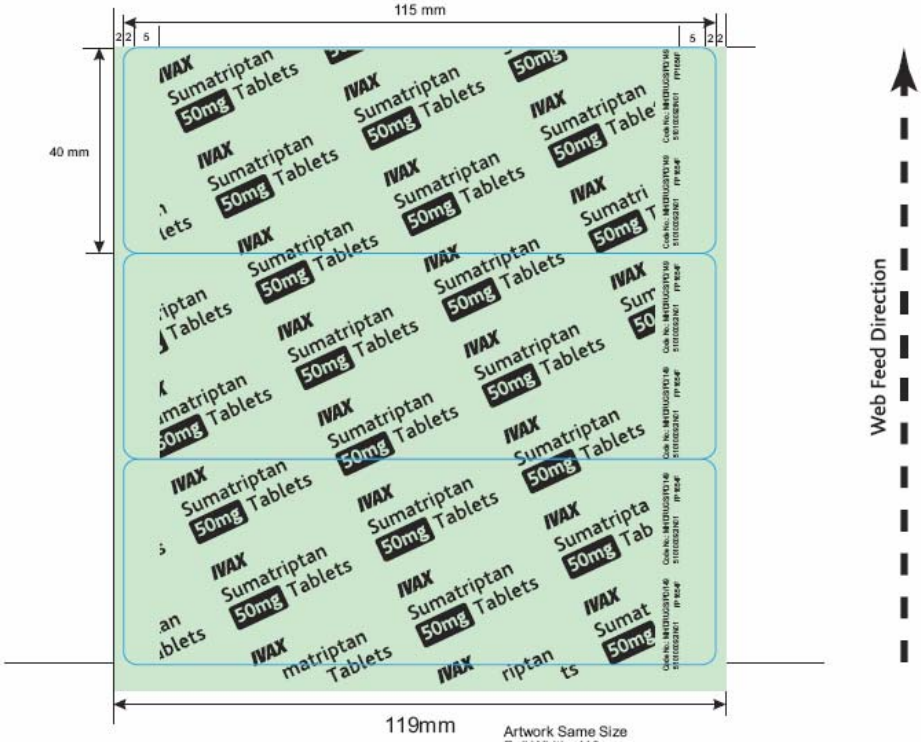

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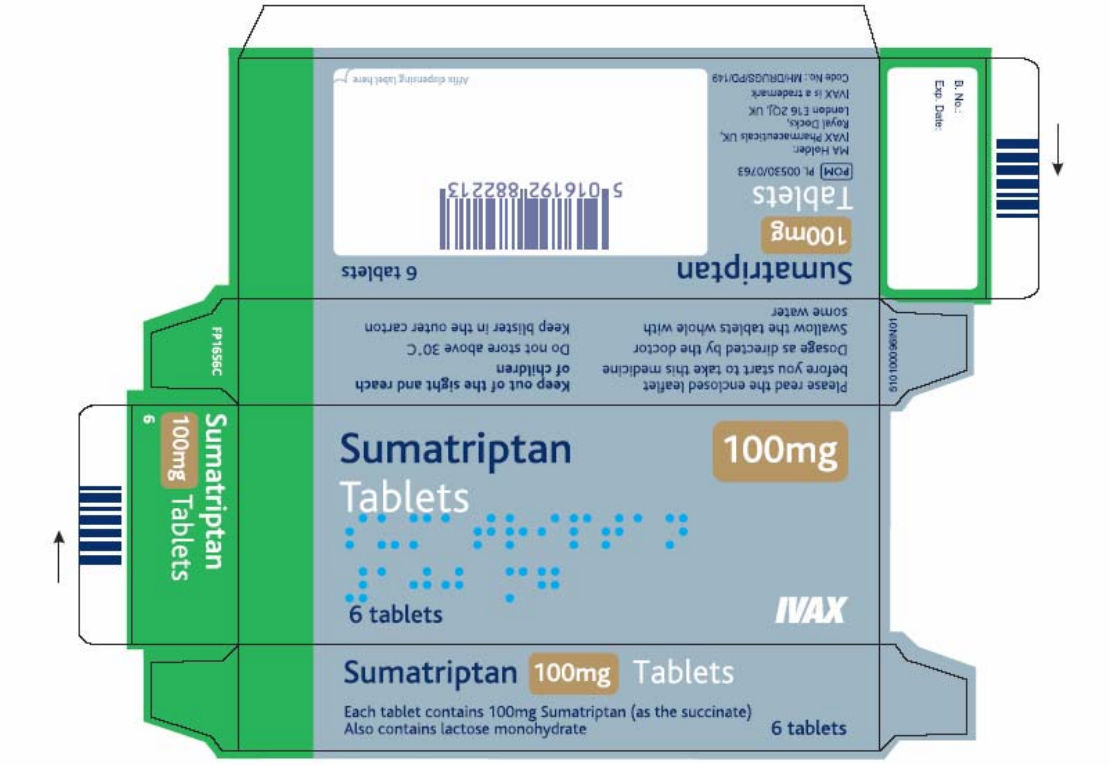

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Last Colour Sep Date: 9/11/04		Artworker's Signature:

Other information:
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