



Public Assessment Report
Mutual Recognition Procedure

Sumatriptan 50mg Tablets
Sumatriptan 100mg Tablets

UK/H/0940-1/001-2/MR
UK licence no: PL 21621/0001-2, 0006-7

J & P Pharma UK Limited

LAY SUMMARY

The MHRA granted J & P Pharma UK Limited Marketing Authorisations (licences) for the medicinal products Sumatriptan 50mg and 100mg Tablets on 6th August 2007. These are prescription-only medicines (POM) indicated for the treatment of migraine attacks. It should only be used when migraine attacks have been diagnosed by a doctor. Sumatriptan should not be used for common headaches.

Sumatriptan belongs to a group of medicines called triptans (5HT receptor agonists).

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 outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 3
Module 2: Summary of Product Characteristics	Page 4
Module 3: Product Information Leaflets	Page 22
Module 4: Labelling	Page 24
Module 5: Scientific Discussion	Page 28
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6	Steps taken after initial procedure

Module 1

Product Name	Sumatriptan 50mg and 100mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Sumatriptan succinate
Form	Film-Coated Tablets
Strength	50mg and 100mg
MA Holder	J&P Pharma UK Limited, Dorset House Regent Park, 297 Kingston Road, Leatherhead, Surrey, KT22 7PL, UK
Reference Member State (RMS)	UK
CMS	PL 21621/0001-2: Austria, Belgium, Denmark, Finland, France, Italy, Luxembourg, The Netherlands, Sweden PL 21621/0006-7: Bulgaria, Czech Republic, Hungary, Slovakia
Procedure Number	UK/H/0940-1/001-2/MR
Timetable	Day 90 – 6 th August 2007

Module 2

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 70 mg sumatriptan succinate).

Excipients: lactose monohydrate (123.5 mg), cochineal red (E124).

For full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sumatriptan 50 mg tablets are light pink, film-coated, oblong, biconvex tablets with a scoreline. The tablet can be divided into equal halves

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

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.

Sumatriptan Tablets 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.

Adults only: 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 and adolescents (under 18 years of age):

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

Elderly (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.

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.

Renal impairment:

Administer with caution.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients, including E124-cochineal red which may cause allergic reactions.

Sumatriptan must not be given to patients who have had myocardial infarction or have ischemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or signs consistent with ischemic heart disease.

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

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

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

The concomitant administration of ergotamine, or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine₁ (5-HT₁) receptor agonist is contraindicated (see Section 4.5).

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated. [product name] must 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.

Sumatriptan should be given with caution to patients with a history of epilepsy, brain damage or other risk factors which lower the seizure threshold, as seizures have been reported in association with sumatriptan (see section 4.8).

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

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

If concomitant treatment with sumatriptan and an SSRI/SRNI is clinically warranted, appropriate observation of the patient is advised (See Section 4.5).

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.

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, 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 or another triptan/5-HT-1 receptor agonist. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated (see section 4.3)

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations or another triptan/5-HT-1 receptor agonist is not known. This will also depend on the doses and type of products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine containing preparations or another triptan/5-HT-1 receptor agonist before administering sumatriptan. Conversely it is advised to wait at least six hours following use of sumatriptan before administering an ergotamine containing product and at least 24 hours before administering another triptan/5-HT1 receptor agonist (see section 4.3)

As interaction may occur between sumatriptan and monoamine oxidase inhibitors and concomitant administration is contraindicated (see section 4.3). Rarely, an interaction may occur between sumatriptan and SSRIs.

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see Section 4.4).

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

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

4.6. Pregnancy and lactation

Pregnancy

Post-marketing data on the use of sumatriptan during the first trimester are available from more than 1000 women. Although these data do not contain sufficient information for a definitive conclusion to be reached, they do not indicate an increased risk of congenital defects. Experience of the use of sumatriptan in the second and third trimester is limited. Up to now, animal studies do not indicate teratogenicity or harmful effects during peri- and post-natal development. However, in rabbits, embryofetal viability may be influenced (see section 5.3). Administration of [product name] should only be considered if the expected benefits for the mother outweigh any possible risk for the unborn child

Lactation

Sumatriptan is excreted into breast milk. Exposure of the child can be minimized by avoiding breast-feeding for 12 hours after administration of sumatriptan

4.7. Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with sumatriptan tablets. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

4.8. Undesirable Effects

Adverse drug reactions are listed below by MedDRA body system organ class and frequency. Frequencies are defined as:

Very Common: > 1/10

Common: > 1/100, < 1/10

Uncommon: > 1/1,000, < 1/100

Rare: > 1/10,000, < 1/1,000

Very rare: < 1/10,000 including isolated reports

CLINICAL TRIAL DATA

Nervous system disorders

Common: Tingling, dizziness, drowsiness.

Vascular disorders

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

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

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

General disorders and administration site conditions

Common: Pain, sensations of heat, pressure or tightness (these events are usually transient and may be intense and can affect any part of the body including the chest and throat). *Uncommon:* Feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).

Investigations

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

POST-MARKETING DATA

Immune system disorders

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

Nervous system disorders

Very rare: Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures there are also reports in patients where no such predisposing factors are apparent. Nystagmus, scotoma, tremor, dystonia.

Eye disorders

Very rare: Flickering, diplopia, reduced vision. Loss of vision including reports of permanent defects. However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders

Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see sections 4.3 and 4.4).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal disorders

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 adverse effects have been observed other than those mentioned in section 4.8.

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

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

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 (5HT_{1D}) receptor agonist with no effect on other 5HT receptor (5-HT₂-5-HT₇) subtypes. The vascular 5-HT_{1D} receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man.

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

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.

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 to 17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 12-17 years was similar to that reported from studies in the adult population.

5.2 Pharmacokinetic Properties

Following oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After 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

In a fertility study in the rat, a reduction in the success of insemination was seen on exposure to concentrations higher than the maximum exposure in humans. In rabbits embryoletality was observed, without marked teratogenic effects. Sumatriptan was devoid of genotoxic and carcinogenic activity in *in-vitro* systems and animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Tablet Core:

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

Film coat:

Hypromellose, macrogol 6000, talc, titanium dioxide (E171), cochineal red (E124), triethyl citrate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

This medicinal product does not require any special storage condition.

6.5. Nature and contents of container

Polyamide/Alu/PVC/Alu blister.

Pack sizes: 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. 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

PL 21621/0006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg sumatriptan (as 140 mg sumatriptan succinate).

Excipients: lactose monohydrate (247 mg).

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.

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.

Sumatriptan Tablets 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.

Adults only: 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 and adolescents (under 18 years of age):

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

Elderly (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.

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.

Renal impairment:

Administer with caution.

4.3. Contraindications

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

Sumatriptan must not be given to patients who have had myocardial infarction or have ischemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or sign consistent with ischemic heart disease.

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

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

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

The concomitant administration of ergotamine, or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine₁ (5-HT₁) receptor agonist is contraindicated (see Section 4.5).

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated. [product name] must 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.

Sumatriptan should be given with caution to patients with a history of epilepsy, brain damage or other risk factors which lower the seizure threshold, as seizures have been reported in association with sumatriptan (see section 4.8).

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

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

If concomitant treatment with sumatriptan and an SSRI/SRNI is clinically warranted, appropriate observation of the patient is advised (See Section 4.5).

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.

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, 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 or another triptan/5-HT-1 receptor agonist. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated (see section 4.3)

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations or another triptan/5-HT-1 receptor agonist is not known. This will also depend on the doses and type of products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine containing preparations or another triptan/5-HT-1 receptor agonist before administering sumatriptan. Conversely it is advised to wait at least six hours following use of sumatriptan before administering an ergotamine containing product and at least 24 hours before administering another triptan/5-HT1 receptor agonist (see section 4.3)

As interaction may occur between sumatriptan and monoamine oxidase inhibitors and concomitant administration is contraindicated (see section 4.3). Rarely, an interaction may occur between sumatriptan and SSRIs.

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see Section 4.4).

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

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

4.6. Pregnancy and lactation

Pregnancy

Post-marketing data on the use of sumatriptan during the first trimester are available from more than 1000 women. Although these data do not contain sufficient information for a definitive conclusion to be reached, they do not indicate an increased risk of congenital defects. Experience of the use of sumatriptan in the second and third trimester is limited. Up to now, animal studies do not indicate teratogenicity or harmful effects during peri- and post-natal development. However, in rabbits, embryofetal viability may be influenced (see section 5.3). Administration of [product name] should only be considered if the expected benefits for the mother outweigh any possible risk for the unborn child

Lactation

Sumatriptan is excreted into breast milk. Exposure of the child can be minimized by avoiding breast-feeding for 12 hours after administration of sumatriptan

4.7. Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with sumatriptan tablets. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

4.8. Undesirable Effects

Adverse drug reactions are listed below by MedDRA body system organ class and frequency. Frequencies are defined as:

Very Common: > 1/10

Common: > 1/100, < 1/10

Uncommon: > 1/1,000, < 1/100

Rare: > 1/10,000, < 1/1,000

Very rare: < 1/10,000 including isolated reports

CLINICAL TRIAL DATA

Nervous system disorders

Common: Tingling, dizziness, drowsiness.

Vascular disorders

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

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

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

General disorders and administration site conditions

Common: Pain, sensations of heat, pressure or tightness (these events are usually transient and may be intense and can affect any part of the body including the chest and throat). *Uncommon:* Feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).

Investigations

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

POST-MARKETING DATA

Immune system disorders

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

Nervous system disorders

Very rare: Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures there are also reports in patients where no such predisposing factors are apparent. Nystagmus, scotoma, tremor, dystonia.

Eye disorders

Very rare: Flickering, diplopia, reduced vision. Loss of vision including reports of permanent defects. However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders

Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see sections 4.3 and 4.4).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal disorders

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 adverse effects have been observed other than those mentioned in section 4.8.

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

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

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 (5HT_{1D}) receptor agonist with no effect on other 5HT receptor (5-HT₂-5-HT₇) subtypes. The vascular 5-HT_{1D} receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man.

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

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.

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 to 17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 12-17 years was similar to that reported from studies in the adult population.

5.2 Pharmacokinetic Properties

Following oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After 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

In a fertility study in the rat, a reduction in the success of insemination was seen on exposure to concentrations higher than the maximum exposure in humans. In rabbits embryoletality was observed, without marked teratogenic effects. Sumatriptan was devoid of genotoxic and carcinogenic activity in *in-vitro* systems and animal studies.

6. PHARMACEUTICAL PARTICULARS**6.1. List of Excipients**Tablet Core:

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

Film coat:

Hypromellose, macrogol 6000, talc, titanium dioxide (E171), triethyl citrate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

This medicinal product does not require any special storage condition.

6.5. Nature and contents of container

Polyamide/Alu/PVC/Alu blister.

Pack sizes: 1, 2, 4, 6, 12, 18 or 20 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

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
PL 21621/0007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**10. DATE OF REVISION OF THE TEXT**

Module 3

Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

(Product name)

50 mg and 100 mg film-coated tablets
sumatriptan

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET

1. What [product name] is and what this medicine is used for
2. Before you take [product name]
3. How to take [product name]
4. Possible side effects
5. How to store [product name]
6. Further information

1. WHAT [PRODUCT NAME] IS AND WHAT THIS MEDICINE IS USED FOR

Your medicine comes as a tablet containing sumatriptan. Sumatriptan tablets belong to a group of medicines called triptans (5HT receptor agonists).

[product name] 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.

[product name] should only be used when migraine headaches have been diagnosed by a doctor.

[product name] should not be used for common headaches.

2. BEFORE YOU TAKE [PRODUCT NAME]

Do not take this medicine and tell your doctor if:

- you are **allergic to sumatriptan** or any other ingredients in this tablet, especially E124 – cochineal red in the 50 mg tablet, which may cause allergic reactions
- 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**

- you have significantly **high blood pressure**, or if your blood pressure is high despite medication
- you use, or have recently used, ergotamine, derivatives of **ergotamine** (for migraine, including methysergide), or any triptan/5-hydroxytryptamine 1 (5-HT₁) receptor agonist.
- you use, or have recently used, **MAO inhibitors** (for instance moclobemide for depression or selegiline for Parkinson's disease)

Take special care with [product name]

You must tell your doctor before taking [product name] if:

- you have **liver or kidney problems**
- you have symptoms of heart disease, such as transient chest pain or a feeling of pressure in your chest, which may also radiate towards your throat
- if you are considered to be at risk of developing heart disease (e.g. diabetic, heavy smoker or undergoing nicotine replacement therapy), and particularly if you are a post-menopausal woman or a man over 40 years with these risk factors, your doctor should check your heart function before prescribing [product name]. In very rare cases serious heart conditions have occurred after taking Sumatriptan, even if no signs of any heart disease were found. Contact your doctor for advice if you have any concerns
- if you have epilepsy, a history of seizures or any other disease which reduces your seizure threshold

Excessive use of sumatriptan (repeated use over several consecutive days) constitutes incorrect use of this medicine and may cause an increase in side effects and lead to chronic headaches requiring the temporary discontinuation of treatment. **Consult your doctor if you start having too frequent or daily headaches as you may suffer from medication overuse headache.**

Taking other medicines

Please tell your doctor if you:

- are taking medicines containing ergotamine or methysergide (to treat migraine)
- are taking MAO inhibitors (e.g. moclobemide for depression or selegiline for Parkinson's disease) or have stopped MAOI treatment in the last 2 weeks
- are taking lithium (for manic/depressive (bipolar) disorders)
- are taking selective serotonin re-uptake inhibitors (SSRI's for depression and other mental conditions), serotonin noradrenaline reuptake inhibitors (SNRIs), or herbal remedies containing St. Johns wort (*Hypericum perforatum*)
- are taking any sulphonamides

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription, herbal medicines, or natural products/remedies.

Pregnancy and breastfeeding

Experience of use during pregnancy is limited. Therefore, ask your doctor or pharmacist for advice before taking [product name] during pregnancy.

Sumatriptan passes into breast milk. Therefore, breast-feeding should be avoided for 12 hours after taking [product name].

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

Driving and using machines

Sumatriptan may make you feel drowsy. If you are affected, do not drive or operate machinery.

Important information about some of the ingredients of [product name]

[product name] contains **lactose**. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE [PRODUCT NAME]

Always take [product name] exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosage:

Adults

- Take one 50 mg tablet as soon as possible at the start of the migraine. In some cases, a 100 mg dose may be needed (your doctor will tell you which dose to take).
- If your symptoms return, you can take a second tablet after two hours.

Do not take a second dose if the first dose had no effect. Maximum dose is 300 mg in 24 hours.

[product name] should not be used as a preventative.

Swallow the tablet whole with a glass of water.

Please note:

If [product name] 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.

Patients with liver problems should be given a lower dose.

Children (under 12 years), [product name] should not be given to children.

If a child takes your medicine contact your doctor or local hospital immediately. Take the pack and any remaining tablets with you.

Adolescents (12 to 17 years of age)

[product name] is not recommended.

Elderly patients (over 65 years):
[product name] is not recommended.

If you take more [product name] than you should

If you take too much of your medicine contact your doctor, local hospital, or poisoning information centre [to be completed nationally] immediately. Take the pack and any remaining tablets with you.

If you forget to take [product name]

Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like most medicines, [product name] can sometimes cause side effects, although not everybody gets them.

The following side effects are very rare (occurs in less than 1 patient in 10,000) but you should **contact your doctor immediately** and do **not** take another dose:

- Sudden wheeziness, fluttering or tightness in the chest, swelling of eyelids, face or lips, skin rash – red spots or hives (skin lumps), which may be signs of an allergic reaction.
- Fits (usually in people with a history of epilepsy).
- Raynaud's phenomenon, which might appear as paleness or a blue tinge to the skin and/or pain of the fingers, toes, ears, nose or jaw in response to cold or stress.
- Inflammation of the colon (part of the intestine), which may present as lower left-sided tummy pain and/or bloody diarrhoea.

Common side effects (occurs in less than 1 patient in 10, but in more than 1 in 100):

- Flushing (redness of the face lasting a few minutes), dizziness, feelings or weakness, tiredness and drowsiness (important if you are driving or working a machine).
- Short lasting increases in blood pressure soon after taking the medicine
- Feeling sick (nausea) or being sick (vomiting) – when not part of migraine attack.
- Pain, sensations or tingling, heat, heaviness and pressure or tightness. If these effects continue or are particularly severe, especially chest or heart pain which spreads to the arms, tell your doctor immediately as there have been rare reports of such problems being caused by heart attack.

Very rare side effects (could happen to less than 1 in 10,000 people taking it):

- Visual disturbances including flickering, double vision and reduced vision. There have been cases where permanent vision defects have occurred.
- Lowering of blood pressure that can lead to feeling of faintness especially on standing up.
- Slowing or quickening in the speed of your heart beat, palpitations (feeling of fast heart beat), changes in heart rhythm.
- Shaking, tremors or uncontrolled movements

- If you have a blood test to check how your liver is working and have taken [product name], tell your doctor as it may affect the results.
- Seizures in patients with a history of seizures, but also in patients where no such predisposing factors are apparent.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE [PRODUCT NAME]

- **Keep out of the reach and sight of children.**
- This medicinal product does not require any special storage conditions.
- Do not use [product name] after the expiry date which is stated on the carton after {abbreviation used for expiry date}. The expiry date refers to the last day of that month.
- Do not use [product name] if you notice any visual damage to [product name].
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What [product name] contains

For 50 mg:

The active substance is sumatriptan.

The other ingredients are: lactose monohydrate, 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.

For 100 mg:

The active substance is sumatriptan.

The other ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, talc, colloidal anhydrous silica, hypromellose, macrogol 6000, titanium dioxide (E171) and triethyl citrate.

What [product name] looks like and contents of the pack

Film-coated tablet

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

Pack sizes: 1, 2, 4, 6, 12 or 18 tablets.

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

Pack sizes: 1, 2, 3, 4, 6, 12, 18 or 20 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: [To be completed nationally]

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

This medicinal product is authorized in the Member States of the EEA under the following names:

Austria: [product name]

Belgium: [product name]

Denmark: [product name]

Finland: [product name]

France: [product name]

Italy: [product name]

Luxembourg: [product name]

The Netherlands: [product name]

Sweden: [product name]

United Kingdom: [product name]

Date of leaflet preparation: 7 Aug 2007

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING:

carton

1. NAME OF THE MEDICINAL PRODUCT

[product name] 50 mg film-coated tablets
Sumatriptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg sumatriptan (as 70 mg sumatriptan succinate).

3. LIST OF EXCIPIENTS

This tablet contains lactose and cochineal red (E124).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet:

1 tablet
2 tablets
4 tablets
6 tablets
12 tablets
18 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the patient leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP: [MM/YYYY]

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage condition.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

No special requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

50 mg:

13. BATCH NUMBER

Batch: [number]

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

[product name] 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

[product name] 50 mg film-coated tablets
Sumatriptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

3. EXPIRY DATE

EXP: [MM/YYYY]

4. BATCH NUMBER

Batch: [number]

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING:

carton

1. NAME OF THE MEDICINAL PRODUCT

[product name] 100 mg film-coated tablets
Sumatriptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg sumatriptan (as 140 mg sumatriptan succinate)

3. LIST OF EXCIPIENTS

This tablet contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet:

1 tablet
2 tablets
3 tablets
4 tablets
6 tablets
12 tablets
18 tablets
20 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the patient leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP: [MM/YYYY]

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage condition.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

No special requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

100 mg:

13. BATCH NUMBER

Batch: [number]

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

[product name] 100 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

[product name] 100 mg film-coated tablets
Sumatriptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP: [MM/YYYY]

4. BATCH NUMBER

Batch: [number]

5. OTHER

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Sumatriptan 50 and 100mg Tablets and their duplicates for the acute relief of migraine attacks (with or without aura), could be approved. A national marketing authorisation was granted on 8th May 2006.

These are applications made under Article 10.1 of 2001/83 EC, as amended, for Sumatriptan 50 and 100mg Tablets and their duplicates, claiming essential similarity to Imigran 50mg and 100mg Tablets (GlaxoSmithKline, UK) which were granted UK licences over 10 years ago.

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

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Sumatriptan 50mg Tablets Sumatriptan 100mg Tablets
Name(s) of the active substance(s) (INN)	Sumatriptan Succinate
Pharmacotherapeutic classification (ATC code)	Analgesic Selective 5-HT Receptor Agonist (N02 CC01)
Pharmaceutical form and strength(s)	50mg and 100mg Film-Coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/940-1/01-02/MR
Reference Member State	United Kingdom
Member States concerned	PL 21621/0001-2: Austria, Belgium, Denmark, Finland, France, Italy, Luxembourg, The Netherlands, Sweden PL 21621/0006-7: Bulgaria, Czech Republic, Hungary, Slovakia
Marketing Authorisation Number(s)	PL 21621/0001-2 and 0006-7
Name and address of the authorisation holder	J&P Pharma UK Limited, Dorset House Regent Park, 297 Kingston Road, Leatherhead, Surrey, KT22 7PL, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

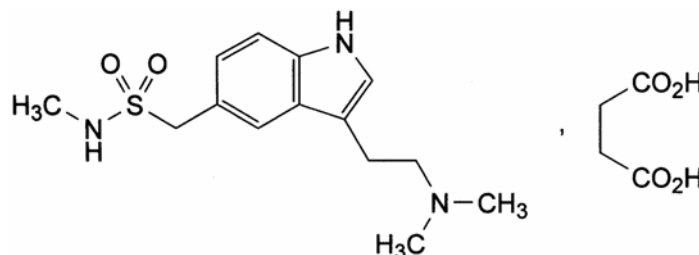
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Sumatriptan succinate

Chemical name: [3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulphonamide hydrogen butanedioate.

Structural formula



Molecular formula: C₁₈H₂₇N₃O₆S

Molecular weight: 413.5

Polymorphism: There is no evidence of polymorphism.

Chirality: There are no chiral centres present so there is no potential for stereoisomerism.

General Properties

Characters: White to almost white powder, freely soluble in methanol, sparingly soluble in water and methylene chloride.

Solubility: Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

Melting point: 165-167°C.

pH (5% in water): 4.5-5.3

Sumatriptan succinate is the subject of a European Pharmacopoeia monograph.

A Certificate of Suitability has been provided covering the manufacture and control of the drug substance sumatriptan succinate. The drug substance specification complies with the Ph Eur monograph, with additional in-house controls for residual solvents and particle size. These are satisfactory.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, talc and colloidal silica anhydrous. The film-coating consisted of hypromellose, Macrogol 6000, talc, titanium dioxide, lake with cochineal red (E124) and triethyl citrate.

All excipients have a respective European Pharmacopoeia monograph, with the exception of lake with cochineal red (which is controlled to a suitable in-house specification). Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph/specifications.

Lactose monohydrate are the only ingredients that comes from an animal source. The lactose used to produce both is sourced from healthy animals under the same conditions as milk for human consumption.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce products containing 50mg and 100mg sumatriptan that are tolerable and which could be considered as generic products to the originator products Imigran 50 and 100 mg Tablets.

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

The rationale and function of each excipient added 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.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results. Comparative impurity studies have also been undertaken.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results at pilot-scale. Additionally, a commitment has been provided that the first full-scale commercial production batches will be validated.

Finished Product Specification

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

All strengths of tablet are packaged in polyvinylchloride/aluminium/polyamide blister strips in pack sizes of 1, 2, 4, 6, 12 and tablets

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

Stability of the product

Stability studies were performed on pilot-scale batches of all strengths of finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 2 years with no storage conditions.

The applicant has committed to providing stability data for the first three production-scale batches of each strength of finished product.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

Conclusion

The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

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

III.3 CLINICAL ASPECTS**Clinical Pharmacology**

With the exception of the bioequivalence study comparing the proposed product to Imigran 100mg Tablets, no formal data are provided and none are required for these applications.

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.

Design:

Single-dose, randomised, crossover, open-label, laboratory-blind study

Test Product: Sumatriptan 100mg tablets

Reference Product: Imigran 100 mg tablets (GlaxoSmithKline UK)

Subjects: 32 finished the study – 18-55yrs, male and female

Washout: 2 weeks

Sampling: 0, 0.166, 0.33, 0.5, 0.75, 1.0, 1.25, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0 and 12 hrs post dose.

Parameters: primary were C_{max} , $AUC_{0-tlast}$ and $AUC_{0-\infty}$; secondary were T_{max} and $T_{1/2}$.

Results:

	C_{max} (ng/mL)	$AUC_{0-tlast}$ (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	T_{max} (hrs)	$T_{1/2}$ (hrs)
Sumatriptan 100mg [Test]	54.8 ± 17.4	231 ± 56.7	243 ± 59.4.	1.88	2.54 ± 0.60
Imigran 100mg [Ref]	52.1 ± 12.3	226 ± 58.3	236 ± 60.0	1.25	2.35 ± 0.52
Point Estimate	105%	102%	103%	0.13%	108%
Ratio 90% CI	98.0; 113	96.6; 108	97.0; 109	-0.25; 0.63	103; 113

Conclusion: The extent and rates of absorption, time to T_{max} and $t_{1/2}$ exhibited indicate that two products may be assumed bioequivalent in terms of the customary confidence intervals.

As the two strengths of the proposed product meet all the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 100mg strength can be extrapolated to the 50mg strength.

Efficacy

No new data on the efficacy of sumatriptan are submitted and none are required for this type of application.

Safety

No new data on the safety of sumatriptan are submitted and none are required for this type of application.

SPC, PIL, Labels

The SPC, PIL and Labels are medically acceptable.

Conclusion

The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

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

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Sumatriptan 100mg Tablets and the originator products Imigran 100mg Tablets (GlaxoSmithKline UK). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 100mg strength can be extrapolated to the 50mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Imigran Tablets.

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 products and the innovator products 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.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome