



**Public Assessment Report**  
**Mutual Recognition Procedure**

**Sumatriptan 50mg Tablets**  
**Sumatriptan 100mg Tablets**

**UK/H/0973/001-002/MR**  
**UK licence no: PL 00289/0588-9**

**TEVA UK Limited**

## LAY SUMMARY

The MHRA granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Sumatriptan 50mg and 100mg Tablets. 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 Marketing Authorisations have been granted.

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## Module 1

<b>Name of the product in the Reference Member State.</b>	Sumatriptan 50mg Tablets Sumatriptan 100mg Tablets
<b>Type of Application</b>	Level 1 Abridged Level 2 Initial/Additional strength Level 3 Generic, Article 10.1 Level 4 Chemical substance Level 5 Prescription only
<b>Active Substance</b>	Sumatriptan succinate
<b>Form</b>	Film-coated Tablets
<b>Strength</b>	50mg and 100mg
<b>MA Holder</b>	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK
<b>RMS</b>	UK
<b>CMS</b>	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Sweden, Slovenia, Slovak Republic, Spain (50mg strength only).
<b>Procedure Number</b>	UK/H/0973/001-001/MR
<b>Timetable</b>	Day 90 – 20 <sup>th</sup> February 2007

## Module 2

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1 NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50 mg Tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:

50 mg: Each film-coated tablet contains 67.5 mg of lactose (as dry substance) as lactose monohydrate.

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Film-coated tablet.

50 mg: Peach to pink, oblong shaped film-coated tablet debossed “5” and “0” on one side and scoreline on each side.

The tablet can be divided into equal halves.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Acute treatment of migraine attacks with or without aura.

##### 4.2 Posology and method of administration

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of migraine 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 after migraine pain has appeared. However, sumatriptan is equally effective when administered at a later time during the attack.

The following recommended dosages should not be exceeded.

##### *Adults*

The recommended dose for adults is a single dose of 50 mg. 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.

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 to treat subsequent attacks.

If symptoms disappear with the first dose but recur, 1 or 2 additional doses may be taken within the next 24 hours, provided that there is a minimum interval of 2 hours between the doses and not more than 300 mg is taken during this period.

The tablets should be swallowed whole with water.

##### *Children (under 12 years of age)*

Sumatriptan is not recommended for use in children below 12 as it has not been studied in children.

##### *Adolescents (12 to 17 years of age)*

The efficacy of sumatriptan in adolescents could not be demonstrated in the clinical studies performed in this age group. Therefore, use in adolescents is not recommended (see section 5.1).

##### *Elderly*

There is limited experience of the use of sumatriptan in patients over the age of 65 years. The pharmacokinetics of the medicinal product in elderly patients has not been studied enough. The use of sumatriptan in patients over 65 years is not recommended until more clinical data are available.

#### *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 insufficiency*

See section 4.4.

### **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 who have ischaemic heart disease, Prinzmetal's variant angina/spasms of the coronary artery or 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).

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

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

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 monoamine oxidase inhibitors.

### **4.4 Special warnings and precautions for use**

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

Sumatriptan is not indicated for use in 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).

Following administration, sumatriptan can be associated with transient symptoms such as chest pain and sensations of tightness which may be intense and may also be felt in the throat area (see section 4.8.). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan are to be given and an appropriate evaluation must be carried out.

Sumatriptan should not be prescribed to patients with risk factors for ischaemic heart disease, including diabetics, heavy smokers or patients on nicotine substitution therapy without prior cardiovascular evaluation (see section 4.3.). Special consideration should be given to post-menopausal women and to men over the age of 40 who have 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 lack of co-ordination after using selective serotonin re-uptake inhibitors (SSRI) and sumatriptan. If the simultaneous use of sumatriptan and SSRIs is clinically justified, appropriate observation of the patient is advised (see section 4.5).

Sumatriptan should be administered with caution to patients with conditions which may affect the absorption, metabolism or excretion of the medicine, such as impaired hepatic or renal function.

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

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. The strength of the reaction ranges from a skin reaction to anaphylaxis. Evidence of cross-allergy is limited, but sumatriptan should nevertheless be administered with caution to such patients.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH (medication overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 amount of patients.

The recommended dosage should not be exceeded.

Sumatriptan Film-coated Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### **4.5 Interaction 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.

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.

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**

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, embryofetal 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 fetus.

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

#### **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 events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1000$ ) and very rare ( $< 1/10,000$ ) including isolated reports.

##### Clinical Trial Data

##### **Nervous system disorders**

*Common:* Tingling, dizziness, drowsiness.

##### **Vascular disorders**

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

##### **Gastrointestinal 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.

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

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* Analgesics: antimigraine preparations: selective serotonin (5-HT<sub>1</sub>) receptor agonists  
*ATC code:* N02CC01

Sumatriptan is a specific and selective agonist of the vascular 5-hydroxytryptamine<sub>1</sub> receptor, with no effect on other 5-HT receptor sub-types. Receptors of this type have mainly been found in cranial blood vessels. In animals, sumatriptan selectively causes vasoconstriction in the circulation of the carotid artery, which supplies blood to extracranial and intracranial tissues such as the meninges. The dilatation of these vessels is thought to be the underlying mechanism of migraine in humans. The results of tests on animals indicate that sumatriptan also inhibits the activity of the trigeminal nerve. Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine-inhibiting effect of sumatriptan in humans.

The clinical response begins about 30 minutes after oral administration of a 100 mg dose. 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.

Sumatriptan is effective for the acute treatment of migraine attacks that occur during menstruation in women, i.e. in the period from 3 days before to 5 days after the beginning of menstruation.

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 is achieved after 45 minutes. The mean peak concentration in plasma after a dose of 100 mg is 54 ng/ml. The mean absolute oral 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.

Binding to plasma protein is low (14 – 21 %) and the mean volume of distribution 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. In patients with hepatic insufficiency, pre-systemic clearance after oral administration is reduced, resulting in an increase in the plasma levels of sumatriptan. 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 5-HT<sub>1</sub> or 5-HT<sub>2</sub> activity. Minor metabolites have not been identified. Migraine attacks do not appear to have a significant effect on the pharmacokinetics of orally administered sumatriptan.

### 5.3 Preclinical safety data

Experimental studies on acute and chronic toxicity gave no evidence on toxic effects in range of human therapeutic doses.

In a rat fertility study, a reduction in the success of insemination was seen at exposures sufficiently in excess of the maximum human exposure.

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

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

50 mg

#### Core

Lactose monohydrate

Croscarmellose sodium

Cellulose, microcrystalline

Silica colloidal anhydrous

Magnesium stearate

Coating – Opadry II 33G23092 peach

Hypromellose E464

Titanium dioxide E171

Lactose monohydrate

Macrogol 3000

Glycerol triacetate

Iron oxide red E172

Iron oxide yellow E172

Iron oxide black E172

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Transparent or white opaque PVC/PVdC aluminium blisters.

50 mg: Blisters of 2, 3, 4, 6, 12,18, 24, 30 and 50 film-coated tablets.

### **6.6 Special precautions for disposal**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

TEVA UK Limited

Brampton Road

Hampden Park

Eastbourne

East Sussex

BN22 9AG

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 00289/0588

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

## **10 DATE OF REVISION OF THE TEXT**

20/02/2008

**SUMMARY OF PRODUCT CHARACTERISTICS****1 NAME OF THE MEDICINAL PRODUCT**

Sumatriptan 100 mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

**Excipients:**

100 mg: Each film-coated tablet contains 135.1 mg of lactose (as dry substance) as lactose monohydrate.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet.

100 mg: White to off-white, oblong shaped film-coated tablet debossed "100" on one side and plain on the other.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

Acute treatment of migraine attacks with or without aura.

**4.2 Posology and method of administration**

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of migraine 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 after migraine pain has appeared. However, sumatriptan is equally effective when administered at a later time during the attack.

The following recommended dosages should not be exceeded.

*Adults*

The recommended dose for adults is a single dose of 50 mg. 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.

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 to treat subsequent attacks.

If symptoms disappear with the first dose but recur, 1 or 2 additional doses may be taken within the next 24 hours, provided that there is a minimum interval of 2 hours between the doses and not more than 300 mg is taken during this period.

The tablets should be swallowed whole with water.

*Children (under 12 years of age)*

Sumatriptan is not recommended for use in children below 12 as it has not been studied in children.

*Adolescents (12 to 17 years of age)*

The efficacy of sumatriptan in adolescents could not be demonstrated in the clinical studies performed in this age group. Therefore, use in adolescents is not recommended (see section 5.1).

*Elderly*

There is limited experience of the use of sumatriptan in patients over the age of 65 years. The pharmacokinetics of the medicinal product in elderly patients has not been studied enough. The use of sumatriptan in patients over 65 years is not recommended until more clinical data are available.

*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 insufficiency*

See section 4.4.

**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 who have ischaemic heart disease, Prinzmetal's variant angina/spasms of the coronary artery or 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).

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

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

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 monoamine oxidase inhibitors.

**4.4 Special warnings and precautions for use**

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

Sumatriptan is not indicated for use in 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).

Following administration, sumatriptan can be associated with transient symptoms such as chest pain and sensations of tightness which may be intense and may also be felt in the throat area (see section 4.8.). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan are to be given and an appropriate evaluation must be carried out.

Sumatriptan should not be prescribed to patients with risk factors for ischaemic heart disease, including diabetics, heavy smokers or patients on nicotine substitution therapy without prior cardiovascular evaluation (see section 4.3.). Special consideration should be given to post-menopausal women and to men over the age of 40 who have 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 lack of co-ordination after using selective serotonin re-uptake inhibitors (SSRI) and sumatriptan. If the simultaneous use of sumatriptan and SSRIs is clinically justified, appropriate observation of the patient is advised (see section 4.5).

Sumatriptan should be administered with caution to patients with conditions which may affect the absorption, metabolism or excretion of the medicine, such as impaired hepatic or renal function.

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

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. The strength of the reaction ranges from a skin reaction to anaphylaxis.

Evidence of cross-allergy is limited, but sumatriptan should nevertheless be administered with caution to such patients.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH (medication overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 amount of patients.

The recommended dosage should not be exceeded.

Sumatriptan Film-coated Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### **4.5 Interaction 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.

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.

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**

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, embryofetal 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 fetus.

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

#### **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 events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1000$ ) and very rare ( $< 1/10,000$ ) including isolated reports.

##### Clinical Trial Data

##### **Nervous system disorders**

*Common:* Tingling, dizziness, drowsiness.

##### **Vascular disorders**

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

##### **Gastrointestinal 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.

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

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* Analgesics: antimigraine preparations: selective serotonin (5-HT<sub>1</sub>) receptor agonists

ATC code: N02CC01

Sumatriptan is a specific and selective agonist of the vascular 5-hydroxytryptamine<sub>1</sub> receptor, with no effect on other 5-HT receptor sub-types. Receptors of this type have mainly been found in cranial blood vessels. In animals, sumatriptan selectively causes vasoconstriction in the circulation of the carotid artery, which supplies blood to extracranial and intracranial tissues such as the meninges. The dilatation of these vessels is thought to be the underlying mechanism of migraine in humans. The results of tests on animals indicate that sumatriptan also inhibits the activity of the trigeminal nerve. Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) may explain the migraine-inhibiting effect of sumatriptan in humans.

The clinical response begins about 30 minutes after oral administration of a 100 mg dose.

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.

Sumatriptan is effective for the acute treatment of migraine attacks that occur during menstruation in women, i.e. in the period from 3 days before to 5 days after the beginning of menstruation.

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 is achieved after 45 minutes. The mean peak concentration in plasma after a dose of 100 mg is 54 ng/ml. The mean absolute oral 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.

Binding to plasma protein is low (14 – 21 %) and the mean volume of distribution 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. In patients with hepatic insufficiency, pre-systemic clearance after oral administration is reduced, resulting in an increase in the plasma levels of sumatriptan. 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 5-HT<sub>1</sub> or 5-HT<sub>2</sub> activity. Minor metabolites have not been identified. Migraine attacks do not appear to have a significant effect on the pharmacokinetics of orally administered sumatriptan.

### 5.3 Preclinical safety data

Experimental studies on acute and chronic toxicity gave no evidence on toxic effects in range of human therapeutic doses.

In a rat fertility study, a reduction in the success of insemination was seen at exposures sufficiently in excess of the maximum human exposure.

In rabbits, embryoletality, without marked teratogenic defects, was seen. The significance of these findings for humans is unknown.

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

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

100 mg

Core

Lactose monohydrate

Croscarmellose sodium

Cellulose, microcrystalline

Silica colloidal anhydrous

Magnesium stearate

Coating – Opadry II 33G28707 white

Hypromellose E464

Titanium dioxide E171

Lactose monohydrate

Macrogol 3000

Glycerol triacetate

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Transparent or white opaque PVC/PVdC aluminium blisters.

100 mg: Blisters of 2, 3, 4, 6, 12, 18, 30 and 50 film-coated tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

TEVA UK Limited

Brampton Road

Hampden Park

Eastbourne

East Sussex

BN22 9AG

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00289/0589

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

20/02/2008



## Module 3

### PACKAGE LEAFLET: INFORMATION FOR THE USER Sumatriptan 50 mg and 100 mg Tablets

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

- Keep this leaflet. You may need to read it again.
- If you have 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 effects not listed in this leaflet, please tell your doctor or pharmacist.

#### IN THIS LEAFLET:

1. What Sumatriptan is and what it is used for
2. Before you take Sumatriptan
3. How to take Sumatriptan
4. Possible side effects
5. How to store Sumatriptan
6. Further information

### 1. What Sumatriptan is and what it is used for

- Sumatriptan belongs to the group of antimigraine preparations. The active substance of Sumatriptan Film-coated Tablets is sumatriptan, a 5-HT<sub>1</sub> receptor agonist.
- Migraine headaches are thought to result from the dilatation of blood vessels. Sumatriptan constricts these blood vessels, thus relieving the migraine headache.
- Sumatriptan is used to treat migraine attacks with or without aura (a warning sensation that usually involves visual distortions, such as light-flashes, zigzag lines, stars, or waves).

### 2. Before you take Sumatriptan

#### Do NOT take Sumatriptan

- if you are allergic (hypersensitive) to sumatriptan or any of the other ingredients of Sumatriptan;
- if you have had a heart attack;
- if you have any heart disease;
- if you have symptoms that might indicate heart disease, such as temporary chest pain or a sensation of pressure in your chest;
- if you have a history of stroke or transient ischaemic attack (TIA, a minor form of stroke that lasts less than 24 hrs);
- if you have blood circulation problems in your legs that cause cramps like pains when you walk (called peripheral vascular disease);
- if you have significantly high blood pressure, or if your blood pressure is high despite medication;
- if you have severe liver problems;
- if you use or have recently used medicines containing ergotamine or ergotamine derivatives (including methysergide);
- if you use or have recently used medicines to treat depression that belong to the group known as monoamine oxidase (MAO) inhibitors.

If you think that you may have any of these problems, or if you are in any doubt at all, contact your doctor before taking Sumatriptan.

### Take special care with Sumatriptan

- Before you are prescribed Sumatriptan your physician will establish whether your headache is caused by migraine and not by any other condition.

Contact your doctor before starting to use this medicine if any of the following applies to you:

- if you know that you have problems with your liver or kidneys;
- if you have been diagnosed with epilepsy or any other disease that reduces the threshold for epileptic fits;
- if you know that you are allergic to antibacterial medicines that belong to the group of sulphonamides;
- if you have controlled high blood pressure as is in a small number of cases sumatriptan has been seen to increase blood pressure;
- if you are taking Selective Serotonin Reuptake Inhibitors (SSRI). Hyperreflexia and lack-of coordination has been observed after concomitant use of Selective Serotonin Reuptake Inhibitors and sumatriptan;
- if you experience pain and/or tightness in the chest or throat. These effects are usually short lasting. If they however persist and you are concerned, or they become severe, contact your doctor immediately for advice;
- if you experience chronic daily headaches. Taking Sumatriptan too often may namely result in developing a chronic headache. In such cases you should contact your doctor as you may have to stop taking Sumatriptan;
- 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 Sumatriptan. 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.

### Taking other medicines

Certain medicines may influence the effectiveness of Sumatriptan, and Sumatriptan may influence the effectiveness of other medicines. Contact your doctor if you take:

- other medicines against migraine, such as ergotamine or similar medicines;
- medicines to treat depression (MAO inhibitors or serotonin re-uptake inhibitors);
- medicines to treat manic/depressive (bipolar) disorders, such as lithium.

During concomitant use of sumatriptan and herbal preparations containing St. John's Wort (*Hypericum perforatum*) side effects may become more common.

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

### Pregnancy and breast-feeding

*Pregnancy:*

- Ask your doctor or pharmacist for advice before taking this medicine.
- There is only limited information regarding the safety of Sumatriptan in human pregnancy. Up to now, these data do not indicate that there is an increased risk for malformations. It is

recommended that you do not take Sumatriptan during pregnancy, unless instructed by your doctor to do so.

*Breast-feeding:*

- Ask your doctor or pharmacist for advice about taking this medicine whilst breast-feeding.
- Sumatriptan is excreted into breast milk. You can minimise the exposure of your baby by avoiding breast-feeding for 12 hours after administration of Sumatriptan, during which time any breast milk expressed should be discarded.

**Driving and using machines**

- Migraine itself or its treatment with Sumatriptan may cause drowsiness. Do not drive or operate machinery if you are affected.

**Important information about some of the ingredients of Sumatriptan**

Sumatriptan contains the sugar lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. How to take Sumatriptan

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

Sumatriptan must not be taken to prevent migraine attacks, because it is intended to treat migraine attacks. Sumatriptan must be taken as soon as possible after the migraine headache appears; however, it is equally effective when taken at a later stage of the attack.

The usual dose for adults is 50 mg. For some patients 100 mg may be necessary. If Sumatriptan does not bring immediate relief, it is not beneficial to take more tablets for this attack. Sumatriptan can be used for your next attack. If, after your first dose, your migraine goes away but then returns, you may take another tablet, provided it is at least two hours since you took the first tablet.

Do not take more than 300 mg (six 50 mg tablets, or three 100 mg tablets) in 24 hours. The use of Sumatriptan in children, adolescents and patients over 65 years is not recommended. For patients with mild to moderate liver impairment low doses of 25-50 mg should be considered. Swallow the tablet whole with some water.

**If you take more Sumatriptan than you should**

Overdose symptoms are the same as those listed in section 4 'Possible side effects'. If you have taken too many tablets, contact a doctor or hospital.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines, Sumatriptan can cause side effects, although not everybody gets them. Contact your doctor if you need to discuss these.

The following side effects are possible with the following frequencies:

*Common:* 1 to 10 of every 100 patients may have these

- Drowsiness, dizziness, tingling.
- Temporary increase in blood pressure (arising soon after treatment), flushing.

- Feeling sick (nausea) or being sick (vomiting).
- Sensation of tension. This is generally transient (temporary), but may be strong and may appear in any part of the body, including chest and throat.
- Pain, sensation of heat, pressure, tightness or anxiety.
- These symptoms may be strong and they may appear in any part of the body, including chest and throat
- Feeling of weakness, tiredness

*Very rare:* fewer than 1 in every 10.000 patients may have these

- Allergic reactions of the skin: A skin rash such as red spots or hives (skin lumps). Anaphylaxis (Strong allergic reactions such as swelling of eyelids, face or lips and sudden wheeziness, fluttering or tightness in the chest).  
If any strong allergic reaction appears, stop taking Sumatriptan and contact your doctor immediately.
  - Nystagmus (involuntary back- and forth-movement of the eyeball), scotoma (dark spots in the field of vision), tremor and dystonia (involuntary muscle contractions).  
Fits - usually in people with a history of epilepsy.
  - Visual disturbances (flickering, diplopia, reduced vision, loss of vision including permanent defect), although these may be caused by the migraine attack itself.
  - Racing heart, slow heartbeat, palpitations, irregular heartbeat, and serious complications of the coronary artery, heart attack, transient ischaemic ECG changes.
  - Decrease in blood pressure, which is a disease characterised by signs of 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 (Raynaud's phenomenon).
  - Inflammation of the colon (part of the intestine), which may present as lower left-sided stomach-ache and bloody diarrhoea.
  - Neck stiffness.
  - If you have a blood test to check your liver function, Sumatriptan may affect your results.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Sumatriptan

Keep Sumatriptan out of the reach and sight of children. This medicinal product does not require any special storage conditions. Do not use Sumatriptan after the expiry date shown on the carton/blister. The expiry date refers to the last day of that month.

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 Sumatriptan contains

- The active substance is sumatriptan. Each tablet contains either 50 mg or 100 mg of sumatriptan (as succinate).
- The other ingredients are:
  - Tablet core: lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, microcrystalline cellulose and magnesium stearate
  - Tablet coating: hypromellose, lactose monohydrate, titanium dioxide (E171), macrogol 3000 and glycerol triacetate. The 50 mg tablets also contain iron oxides red, yellow and black (E172).

### What Sumatriptan looks like and contents of the pack

- Sumatriptan 50 mg Tablets are peach to pink, oblong-shaped film-coated tablets debossed “5” and “0” on one side with scoreline on each side. The tablet can be divided into equal halves.
- Sumatriptan 100 mg Tablets are white to off-white, oblong-shaped film-coated tablets debossed “100” on one side and plain on the other.

The product is available in pack sizes of 2, 3, 4, 6, 12, 18, 30 and 50 tablets.  
The 50 mg product is also available in pack sizes of 24 tablets.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

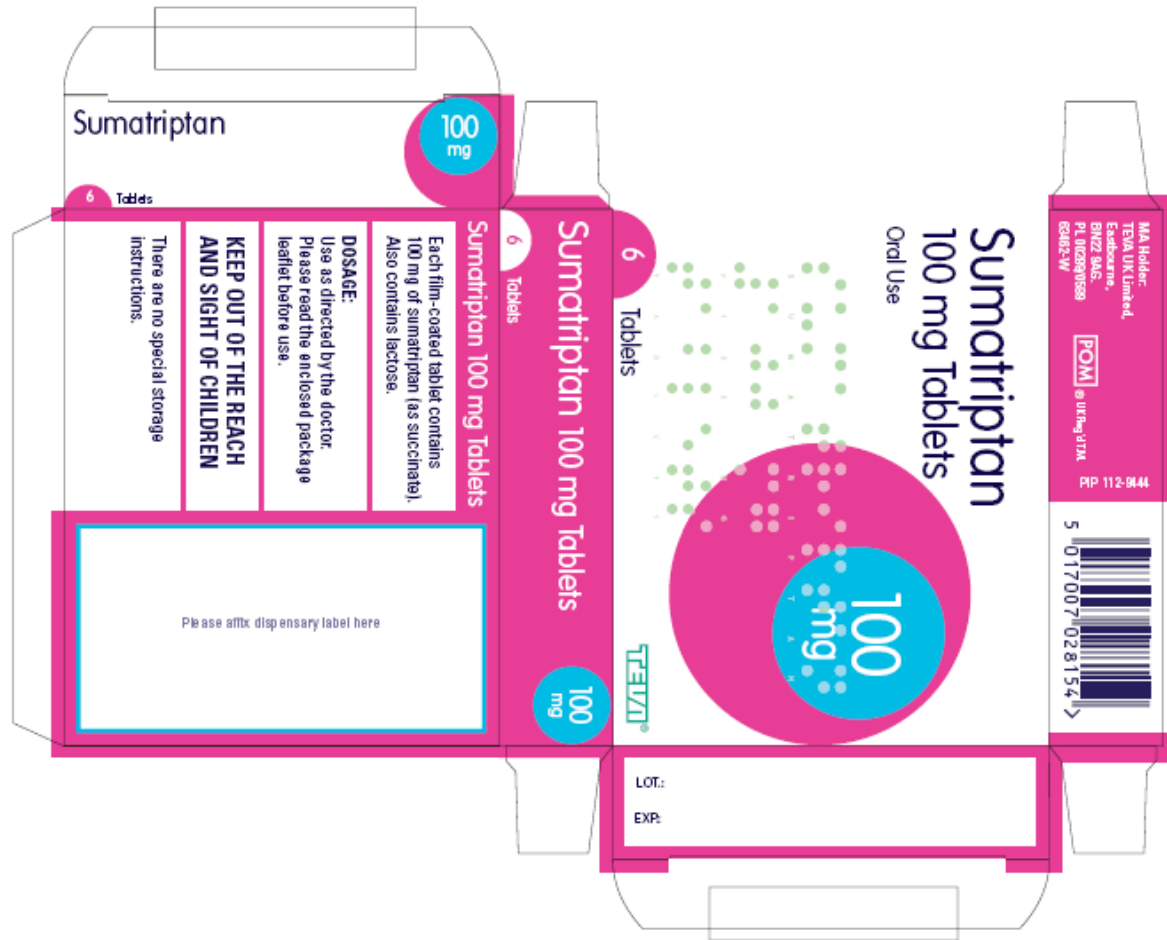
TEVA UK Limited, Eastbourne, BN22 9AG

The leaflet was last approved in {MM/YYYY}

PL 00289/0588  
PL 00289/0589



**Carton- Sumatriptan 100mg Tablets**



**Blister Foil- Sumatriptan 100mg Tablets**



## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted marketing authorisations for Sumatriptan 50mg and 100mg Tablets for the acute relief of migraine attacks (with or without aura) could be approved. National marketing authorisations were granted on 6<sup>th</sup> July 2006.

These are applications made under Article 10.1 of 2001/83 EC, as amended, for Sumatriptan 50mg and 100mg Tablets and have been shown to be generic medicinal products of the original products Imigran 50mg and 100mg Tablets (GlaxoSmithKline, UK) which were granted licences over 10 years ago.

Sumatriptan is a specific and selective agonist of vascular 5-hydroxytryptamine<sub>1</sub> 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 dilations 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. 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.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.



**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)	Nervous system, analgesics, antimigraine preparations, selective serotonin (5HT <sub>1</sub> ) agonists (N02C C01)
Pharmaceutical form and strength(s)	Film-coated tablet, 50mg and 100mg
Reference numbers for the Mutual Recognition Procedure	UK/H/973/01-02/MR
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Germany, Denmark, Greece, Spain (50 mg strength only), Finland, France, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Sweden, Slovenia, Slovakia
Marketing Authorisation Number(s)	PL 00289/0588 PL 00289/0589
Name and address of the authorisation holder	TEVA UK Limited Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG, United Kingdom

### III SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 Quality aspects

##### S. Active substance

rINN/Ph.Eur name: Sumatriptan succinate

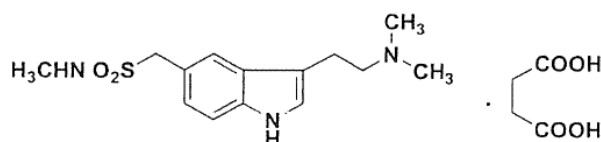
Chemical name: [3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulphonamide hydrogen butanedioate

3-[2-(Dimethylamino)ethyl]-1*H*-indole]-*N*-Methyl-5-sulphonamide succinate

3-2(2-Dimethylamino)ethyl]-*N*-Methyl-]-1*H*-indole]-5-sulfonamide succinate

Molecular formula: C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub>S

Molecular weight: 413.5



Structural formula:

Polymorphism: There is no evidence of polymorphism.

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

Characteristics: White to almost white powder.

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

Sumatriptan succinate is the subject of a European Pharmacopoeia monograph.

A DMF has been provided covering the manufacture and control of the drug substance sumatriptan succinate. The drug substance specification complies with the Ph.Eur. monograph. These are satisfactory.

##### P. Medicinal product

###### Other ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, sodium croscarmellose, colloidal anhydrous silica, magnesium stearate, Opadry II white and Opadry II peach and purified water.

All excipients have a respective European Pharmacopoeia monograph, with the exception of Opadry II white and Opadry II peach (which are controlled to suitable in-house specifications). Satisfactory certificates of analysis have been provided for all the ingredients showing compliance with their respective monograph/specifications.

Lactose monohydrate is the only ingredient that comes from an animal source. The lactose used is sourced from healthy animals under the same conditions as that 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 50mg and 100mg Tablets. 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 been shown to give satisfactory results at pilot-scale. Additionally, a commitment has been provided that the first three full-scale commercial production batches will be validated.

**Finished Product Specification**

The finished product specifications for both strengths are satisfactory. 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**

The product is packed in transparent or opaque white PVC/PVdC-aluminium blisters. For the 50mg strength, each pack contains 2, 3, 4, 6, 12, 18, 24, 30 or 50 tablets (the 100mg strength is the same, apart from not having the 24 pack). The packaging materials comply with the European Pharmacopoeia.

**Stability of the product**

The finished product specification is in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods. The stability studies on the products have been undertaken for 4 batches packed in packaging proposed for marketing. The tablets have been tested for 6 months in accelerated and 24 months in long-term conditions. All batches remained within specifications over the long-term and accelerated periods examined. A shelf-life of 24 months is acceptable.

**Bioequivalence/bioavailability**

A bioequivalence study has been performed on Sumatriptan 100mg Tablets and Imigran 100mg Tablets. Comparable bioavailability was seen in both products. Based on these data it can be considered that the innovator and the generic products are essentially similar.

**III.2 Non-clinical aspects** The applicant's expert provides a sufficiently comprehensive overview of the pharmacology and toxicology of sumatriptan. No new preclinical toxicology data were submitted, which is acceptable given the nature of the application.

**III.3 Clinical aspects**  
**Clinical Pharmacology**

The application contains an adequate review of published clinical data. With the exception of the bioequivalence study comparing the proposed product to Imigran 100mg Tablets, no new toxicology, pharmacokinetic or pharmacodynamic data were submitted for this application and none were 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, 2-way cross-over bioequivalence study

Test product: Sumatriptan 100mg tablets

Reference Product: Imigran 100mg (GlaxoSmithKline UK)

Washout: 7 days

Sampling: 0.166, 0.333, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.9, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 hrs post dose

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

*Results:*

	<b>Sumatriptan test</b>	<b>Imigran reference</b>	<b>Test/Ref Ratio</b>	<b>Test/Ref (90% CI) #</b>
<b><math>AUC_{0-t}</math> (ng/ml h) mean (SD)</b>	190.87 (50.08)	186.84 (34.65)	100.80%	94.98% to 106.99%
<b><math>AUC_{0-inf}</math> (ng/ml h) mean (SD)</b>	199.71 (51.49)	195.38 (35.36)	100.95%	95.34% to 106.89%
<b><math>C_{max}</math> (ng/ml) mean (SD)</b>	46.70 (13.04)	45.85 (11.32)	101.11%	92.42% to 110.62%
<b><math>T_{max}</math> (h) median (range)</b>	1.33 (2.38)	1.33 (1.39)		
<b><math>T_{1/2el}</math> (h) median (range)</b>	2.38 (0.42)	2.48 (0.420)		

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

*Conclusions:*

Both formulations were well tolerated with no relevant safety differences. The test product was accepted as bioequivalent in terms of rate and extent of absorption to the reference product.

As the two strengths of the proposed product 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 an application 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 product and the originator product are interchangeable. Extensive clinical experience with sumatriptan succinate 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

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
11/06/2007	Label & Leaflet-Self Certification	To make dimensional changes to the carton & foil and the removal of "Distributed by TEVA UK Limited" from the 50mg & 100mg cartons.	Approved
05/10/2007	Type II National	To update the SPC and PIL in-line with EU SPC/PIL/Labels approved in the MRP (UK/H/973/01-02/MR)	Approved
25/04/2008	Label & Leaflet-Self Certification	Label and leaflet submission for self certification under article 61(3). Change falls into category no 7 - Updating of statutory warnings in line with new legislation or guidance.	Approved