

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imigran Migraine Relief 50mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 50mg of sumatriptan base as the succinate salt.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink film-coated, triangular shaped, biconvex, tablet debossed "GS 1YM" on one face and '50' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Imigran tablets are indicated for the acute treatment of migraine attacks with or without aura, including the acute treatment of menstrually associated migraine.

4.2 Posology and method of administration

Imigran Migraine Relief is indicated for the acute intermittent treatment of migraine. Imigran Migraine Relief should not be used prophylactically.

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

It is advisable that Imigran Migraine Relief be given as early as possible after the onset of a migraine headache. It is equally effective at whatever stage of the attack it is administered.

Adults only:

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

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

If the patient has responded to the first dose, but the symptoms recur, a second dose may be given in the next 24 hours, provided that not more than 300mg is taken in any 24 hour period. An interval of two hours should generally be allowed to elapse between doses.

The tablets should be swallowed whole with water. Patients with swallowing difficulties may choose to disperse a tablet in a small amount of water before administration. Imigran Migraine Relief dispersed in water have a bitter taste.

Children and Adolescents (under 18 years of age)

Imigran Migraine Relief fast disintegrating tablets have not been studied in adolescents or children (see Clinical Studies).

Elderly (over 65):

Experience of the use of Imigran Migraine Relief 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 Imigran Migraine Relief in patients aged over 65 years is not recommended.

Patients with Hepatic Impairment:

Impairment of hepatic function gives rise to an 80% increase in plasma sumatriptan levels after an oral dose of 100mg. The drug should therefore be used with extreme caution and at reduced dosage in these patients.

Patients with Renal Impairment:

There is no information on the effect of renal impairment.

4.3 Contraindications

Hypersensitivity to any component of the preparation.

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

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

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

The use of sumatriptan in patients with uncontrolled hypertension is contraindicated.

The concomitant administration of ergotamine, or derivatives of ergotamine (including methysergide) is contraindicated (*see Interaction with other medicinal products and other forms of Interaction*).

Concurrent administration of monoamine oxidase inhibitors or use within two weeks of discontinuation of MAOI therapy is contra-indicated.

Until further data are available the use of Imigran is contra-indicated in patients receiving concurrent treatment with certain antidepressants e.g. selective 5-HT reuptake inhibitors (*see Interaction with other Medicinal Products and Other Forms of Interaction*) and lithium.

Imigran Migraine Relief should not be given to diabetic patients.

4.4 Special warnings and precautions for use

Imigran Migraine Relief should only be used where there is a clear diagnosis of migraine.

Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.

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

There have been a number of reports of CVA (stroke, paresis), where a temporal association with sumatriptan intake was seen. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. CVA, TIA).

Imigran Migraine Relief should not be used in patients with underlying cardiac disorders and in patients who, although

asymptomatic, have significant risk factors predisposing to coronary artery disease.

Therefore a careful history to exclude pre-existing cardiac disease should be taken before sumatriptan is prescribed. Evaluations may not identify every patient who has cardiac diseases and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease and in the absence of known risk factors.

Patients in whom undiagnosed coronary artery disease is a possibility on the basis of age or the presence of other risk factors, such as family history of coronary artery disease, tobacco smoking, diabetes, hypercholesterolaemia, should receive the product only with great caution and if the benefit of treatment is judged to outweigh the possible risk. Use of sumatriptan should be carefully considered in patients who may be at risk of thrombotic episodes. There have been rare reports of patients on hormone replacement therapy who have had cardiac ischaemic events.

Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat and arms. These symptoms may mimic angina pectoris but, in patients in whom cardiac investigations have been performed, they have only rarely been found to have been the result of coronary vasospasm. Although rare, the vasospasm may result in arrhythmia including ventricular fibrillation/ischaemia or myocardial infarction. If the patient experiences symptoms which are severe or persistent or are consistent with angina, further doses should not be taken until appropriate investigations have been carried out to check for the possibility of ischaemic changes.

There have been a number of fatalities from ventricular fibrillation and myocardial infarction.

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 administered with caution to patients with conditions, which may affect significantly the absorption, metabolism or excretion of the drug, e.g. impaired hepatic or renal function.

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

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

Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.

The recommended dose of Imigran Migraine Relief should not be exceeded.

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/SNRI is clinically warranted, appropriate observation of the patient is advised (see Interactions).

The concomitant administration of any triptan/5-HT₁ agonist with sumatriptan is not recommended.

Overuse of acute migraine treatments has been associated with the exacerbation of headache (Medication Overuse Headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Studies in healthy subjects show that Imigran does not interact 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 contra-indicated.

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 *Contra-indications*).

There is a risk of CNS toxicity when both MAOI's and SSRI's are given with Imigran; hence concomitant use is contraindicated (see section 4.3).

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 Warnings and Precautions).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Caution should be exercised by considering the expected benefit to the mother against possible risk to the foetus.

Post-marketing data from multiple prospective pregnancy registries have documented the pregnancy outcomes in over 1,000 women exposed to sumatriptan. Although there is insufficient information to draw definitive conclusions, the findings have not detected an increase in the frequency of birth defects nor a consistent pattern of birth defects, amongst women exposed to sumatriptan compared with general population.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000) including isolated reports. The data from clinical trials are estimates. It should be noted that the background rate in comparator groups was not taken into account. Post-marketing data refer to reporting rate rather than true frequency.

Clinical Trial Data:

Nervous System Disorders

Common: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia.

Vascular disorders

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

Gastrointestinal Disorders

Common: Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

Musculoskeletal and Connective Tissue Disorders

The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:

Common: Sensations of heaviness.

General Disorders and Administration Site Conditions

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:

Common: Pain, sensations of heat or cold, pressure or tightness.

The following symptoms are mostly mild to moderate in intensity and transient:

Common: Feelings of weakness, fatigue.

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 anaphylaxis.

Nervous System Disorders

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

Eye disorders

Very rare: Flickering, diplopia, reduced vision. Loss of vision (usually transient). 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, angina, myocardial infarction (*see Section 4.3 Contraindications, Section 4.4 Special warnings and precautions*).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Very rare: Ischaemic colitis.

4.9 Overdose

There have been some reports of overdosage with Imigran Migraine Relief.

Patients have received single injections of up to 12mg subcutaneously without significant adverse effects. Doses up to 16mg subcutaneously and up to 400mg orally were not associated with side effects other than those mentioned. There is no experience of doses greater than these.

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

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

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Selective 5HT₁ receptor agonist.

ATC code: N02CC01.

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5HT_{1d}) receptor agonist with no effect at other 5HT receptor (5HT₂-5HT₇) subtypes. The vascular 5HT_{1d} receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals sumatriptan selectively constricts the carotid arterial circulation, the carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. In addition, evidence from animal studies suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions (cranial vasoconstriction and inhibition of trigeminal nerve activity) may contribute to the anti-migraine action of sumatriptan in humans.

Pharmacodynamic Effects

Clinical response begins 10 to 15 min following a 6 mg subcutaneous injection, 15 min following a 20 mg dose given by intra-nasal administration and around 30 min following a 100 mg ***conventional tablet*** oral dose or 25 mg rectal dose.

Results of two identical, randomised, double-blind placebo controlled studies (Study 1 treating 1330 patients and Study 2 treating 1366 patients) demonstrated that:

- Following administration of the Imigran Fast Disintegrating Tablet (FDT) the onset of pain relief began as early as 30 minutes for patients taking 50mg (19% vs 14% of placebo patients) and 20 minutes for patients taking 100mg (6% vs 4% of placebo patients). The percentage of responders continued to increase until 67% (603/902) of 50mg patients and 72% (649/902) of 100mg subjects achieved pain relief over 2 hours, compared to 42% (375/892) of placebo subjects.
- Onset of “pain free” began as early as 33 minutes for patients taking 50mg (4% vs 2% of placebo patients) and 26 min for patients taking 100mg (2% vs 1% of placebo patients). The percentage of responders continued to increase until 40% (358/902) of 50mg patients and 47% (426/902) of 100mg subjects achieved pain free response over 2 hours, compared to 15% (137/892) of placebo subjects.

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

5.2 Pharmacokinetic properties

Absorption:

Rapid. However bioavailability is low (approximately 14% of a dose), primarily because of presystemic hepatic metabolism and, to a lesser extent, because of incomplete absorption. The rate and extent of absorption are not affected to a clinically significant extent.

Bioavailability is increased by 80% in patients with hepatic impairment.

Distribution:

Sumatriptan is rapidly and extensively distributed to tissues, but passage across the blood-brain barrier is limited.

Protein binding:

In plasma - low (14 to 21%).

Biotransformation:

Hepatic and extensive; approximately 80% of a dose is metabolised. The major metabolite is an inactive indole acetic acid derivative.

Half-life:

Elimination: Approximately 2 hours. One study reported a terminal half-life of approximately 7 hours that became apparent about 12 hours after administration of multiple oral doses, but did not contribute substantially to the overall disposition of the medication.

Onset of action:

Within 30 minutes.

Time to peak concentration:

In serum (single 100mg dose): Approximately 1.5 hours (range, 0.5 to 5 hours). The wide interindividual variability found in pharmacokinetic studies may be related to the appearance of multiple peaks in the concentration over time. Approximately 80% of the maximum value is achieved within 45 minutes.

Peak concentration:

In serum (single 100mg dose): Approximately 54 nanograms per ml; (0.13 micromoles/L) (range 26.7 to 137 nanograms per ml; 0.06 to 0.33 micromoles/L). The C_{max} of sumatriptan is increased by 15% following oral administration of the fast disintegrating tablets with a high fat meal compared with administration of fast disintegrating tablets administered in the fasted state.

Time to peak effect:

Relief of headache (i.e. moderate or severe pain being reduced to mild or no pain)-

Single 100mg dose: Within 2 hours in 50 to 75%, and within 4 hours in an additional 15 to 25% of patients.

Relief of associated symptoms (nausea, vomiting, photophobia, phonophobia)-

Single 100mg dose: Within 2 hours.

Duration of action:

Return of migraine headache occurs within 24 to 48 hours in approximately 40% of patients who initially obtain a beneficial response to sumatriptan, i.e. after moderate or severe headache pain has been reduced to mild or no pain. Whether this represents development of a new migraine or breakthrough of a prolonged migraine after the effects of sumatriptan have worn off has not been established.

Elimination:

Renal, via active renal tubular secretion, following hepatic metabolism. Approximately 80% of a dose is eliminated as metabolites. After oral administration, approximately 57% of a dose is eliminated in the urine (3% of the dose as unchanged sumatriptan, 35% as the indole acetic acid metabolite) and another 38% of the dose is eliminated in the faeces (9% as unchanged sumatriptan and 11% as the indole acetic acid metabolite).

The effects of renal function impairment on clearance of sumatriptan have not been studied. Hepatic impairment produces an increase of 80% in plasma levels after oral dosing.

5.3 Preclinical safety data**Reproduction Toxicity**

In a rat fertility study a reduction in success of insemination was seen at exposures sufficiently in excess of the maximum human exposure. In rabbits embryoletality, without marked teratogenic defects, was seen.

Although no teratogenic effects have been seen in rats or rabbits, reproduction studies in rabbits, using high and maternally toxic doses, associated with blood levels more than fifty times those seen in humans after therapy, have shown an increased incidence of minor variation in the position of certain foetal blood vessels. Reproduction studies performed in rats have revealed no evidence of impaired fertility or postnatal development due to sumatriptan. The relevance for humans of these findings is unknown.

Mutagenicity and Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, anhydrous

Microcrystalline cellulose

Sodium hydrogen carbonate

Croscarmellose sodium

Magnesium stearate

Opadry pink YS-1-1441G, containing hypromellose, titanium dioxide (E171), triacetin and red iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package to protect from light.

6.5 Nature and contents of container

Double foil blister packs contained in a cardboard carton.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (Ireland) Limited

12 Riverwalk

Citywest Business Campus

Dublin 24

Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/110/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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