Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imigran Ftab 50 mg 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 Ftab 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 Ftab should not be used prophylactically. The recommended dose of Imigran Ftab should not be exceeded.
Imigran Ftab is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

It is advisable that Imigran Ftab 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 Ftab is a 50 mg tablet. Some patients may require 100 mg.

If a patient does not respond to the first dose of Imigran Ftab, a second dose should not be taken for the same attack. In these cases the attack can be treated with paracetamol, acetylsalicylic acid or non-steroidal anti-inflammatory drugs. Imigran Ftab 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, provided that there is a minimum interval of 2 hours between the 2 doses. No more than 300 mg should be taken in any 24 hour period.

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 Ftab dispersed in water have a bitter taste.

Paediatric population
The efficacy and safety of Imigran Ftab in children aged less than 10 years have not been established. No clinical data are available in this age group.

The efficacy and safety of Imigran Ftab in children 10 to 17 years of age have not been demonstrated in the clinical trials performed in this age group. Therefore the use of Imigran Ftab in children 10 to 17 years of age is not recommended (see section 5.1).

Older People (over 65 years of age):
Experience of the use of Imigran Ftab 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 Ftab in patients aged over 65 years is not recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed is section 6.1.

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 ischaemic 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 moderate and severe hypertension and mild uncontrolled hypertension is contraindicated.

The concomitant administration of ergotamine, or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist is contraindicated (see section 4.5).

Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated. Imigran Ftab must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Imigran Ftab 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.

Before treating with sumatriptan, care should be taken to exclude potentially serious neurological conditions (e.g. CVA, TIA) if the patient presents with atypical symptoms or if they have not received an appropriate diagnosis for sumatriptan use.

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

Sumatriptan should be given with caution to patients with mild controlled hypertension, since transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients (see section 4.3).

Sumatriptan should not be given to patients with risk factors for ischaemic heart disease, including those patients who are heavy smokers or users of nicotine substitution therapies, without prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease (see section 4.8).

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 section 4.5)

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 (Child Pugh grade A or B; see section 5.2) or renal function (see section 5.2).

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

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

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

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 medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

This medicine contains less than 1mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 preparations containing ergotamine or another triptan/5-HT_1 receptor agonist. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contra-indicated (see section 4.3).

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparationsor 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 agonistbefore administering sumatriptan. Conversely, it is advised to wait at least 6 hours following use of sumatriptan before administering an ergotamine containing product and at least 24 hours before administering another triptan/5-HT_1 receptor agonist.

An interaction may occur between sumatriptan and MAOIs and concomitant administration 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 section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:
Post-marketing data on the use of sumatriptan during the first trimester of pregnancy 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 effectsor harmful effects on peri- and postnatal development. However, embryo-foetal viability might be affected in the rabbit (see section 5.3). Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation:
Sumatriptan is excreted into breast milk, with average relative infant doses of < 4% following administration of a single dose of sumatriptan. Infant exposure can be minimised by avoiding breast-feeding for 12hours after treatment, during which time any breast milk expressed should be discarded.

There have been reports of breast pain and/or nipple pain following sumatriptan intake in breastfeeding women (see section 4.8). The pain was usually transient and disappeared in 3 to 12 hours.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Drowsiness may occur as a result of migraine or its treatment with Imigran Ftab. 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data). Some of the symptoms reported as undesirable effects may be associated symptoms of migraine.

Immune system disorders
Not known: Hypersensitivity reactions ranging from cutaneous hypersensitivity (such as urticaria) to anaphylaxis.

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

Not known: Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are alsoreports in patients where no such predisposing factors are apparent; Tremor, dystonia, nystagmus, scotoma.

Eye disorders
Not known: 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
Not known: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see sections 4.3 and 4.4).

Vascular disorders
Common: Transient increases in blood pressure arising soon after treatment. Flushing.
Not known: Hypotension, Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea.

Gastrointestinal Disorders
Common: Nausea and vomiting occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition.
Not known: Ischaemic colitis, diarrhoea, dysphagia.

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). Myalgia.
Not known: Neck stiffness.
Not known: Arthralgia.

Reproductive system and breast disorders
Rare: Breast pain.

General disorders and administration site conditions

Common: Pain, sensations of heat or cold, 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); feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient).
Not known: Pain trauma activated, pain inflammation activated.

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

Psychiatric disorders
Not known: Anxiety.

Skin and subcutaneous tissue disorders
Not known: Hyperhidrosis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms and signs
Doses up to 100 mg orally were not associated with side effects other than those mentioned.

Treatment
If overdosage with Imigran Ftab occurs, the patient should be monitored for at least 10 hours and standard supportive treatment applied as required. It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of Imigran Ftab.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective $5HT_1$ 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 ($5HT_2$-$5HT_7$) 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, 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 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 minutes 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 Ftab is 50mg, migraine attacks vary in severity both within and between patients. Doses of 25 to 100mg have shown greater efficacy than placebo in clinical trials, but 25mg is statistically significantly less effective than 50 and 100mg.

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in approximately 800children and adolescent migraineurs aged 10 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 10 to 17 years was similar to that reported from studies in the adult population.

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.

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 Cmax 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.

Special populations
Hepatic impairment
Sumatriptan pharmacokinetics after an oral dose (50 mg) and a subcutaneous dose (6 mg) were studied in 8 patients with mild to moderate hepatic impairment matched for sex, age, and weight with 8 healthy subjects. Following an oral dose, sumatriptan plasma exposure (AUC and Cmax) almost doubled (increased approximately 80%) in patients with mild to moderate hepatic impairment compared to the control subjects with normal hepatic function. There was no difference between the patients with hepatic impairment and control subjects after the s.c. dose. This indicates that mild to moderate hepatic impairment reduces presystemic clearance and increases the bioavailability and exposure to sumatriptan compared to healthy subjects.

Following oral administration, pre-systemic clearance is reduced in patients with mild to moderate hepatic impairment and systemic exposure is almost doubled. Since only a portion of the nasal spray dose is swallowed, patients with mild to moderate hepatic impairment could also have higher exposures, but to a lesser extent than observed after oral dosing (see Section 4.4, Warnings and Precautions).

The pharmacokinetics in patients with severe hepatic impairment have not been studied (see Section 4.3 Contraindications and Section 4.4 Warnings and Precautions).

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 embryolethality, 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
Microcrystalline cellulose
Sodium hydrogen carbonate
Croscarmellose sodium
Magnesium stearate
Opadry pink YS-1-1441G, (containing hypromellose, titanium dioxide (E171), triacetin, 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.

6.5 Nature and contents of container

Doublefoil blister packs or child-resistant foil blister pack, 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/008/006

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