Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imigran 20 mg Nasal Spray, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nasal applicator contains 20 mg of sumatriptan in 0.1 ml of solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, solution.

A clear, pale to dark yellow, buffered solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Imigran Nasal Spray is indicated for the acute treatment of migraine attacks with or without aura.

4.2 Posology and method of administration

Imigran Nasal Spray should not be used prophylactically. The recommended dose of Imigran Nasal Spray should not be exceeded.

Imigran Nasal Spray 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 Nasal Spray 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 (18 years of age and over):
The optimal dose of Imigran Nasal Spray is 20 mg for administration into one nostril. However, due to inter/intra patient variability of both the migraine attacks and the absorption of sumatriptan, 10 mg may be effective in some patients.

If a patient does not respond to the first dose of Imigran Nasal Spray, 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 Nasal Spray 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 there is a minimum interval of 2 hours between the two doses.

No more than two Imigran 20 mg Nasal Sprays to be used in any 24 hour period.

Adolescents (12-17 years of age)
Imigran 20 mg Nasal Spray is not recommended for use in adolescents.

Children (under 12 years of age):
Imigran Nasal Spray is not recommended for use in children under 12 years of age due to insufficient data on safety and efficacy.

Older People (over 65 years of age):
There is no experience of the use of Imigran Nasal Spray in patients over 65. The pharmacokinetics in older patients have not been sufficiently studied. Therefore the use of sumatriptan is not recommended until further data are available.

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 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 contra-indicated.

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

Concurrent administration of monoamine oxidase inhibitors (MAOIs)and sumatriptan is contra-indicated.

Imigran must not be used within 2 weeks of discontinuation of therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Imigran Nasal Spray 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 and in adolescents (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).

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

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following 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)*.

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.

4.5 Interaction with other medicinal products and other forms of interactions

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-HT1 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 preparations or another triptan/5-HT1 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-HT1 receptor agonist before 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-HT1 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:
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 effects 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 (≥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.

Adverse events reported in adults have also been observed in adolescents. These include very rare reports of coronary artery vasospasm and myocardial infarction (see section 4.4)

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

Nervous system disorders

Very common: Dysgeusia/unpleasant taste.

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: Following administration of sumatriptan nasal spray mild, transient irritation or burning sensation in the nose or throat or epistaxis have been reported. 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.

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
Single doses of sumatriptan, up to 40 mg intranasally and in excess of 16 mg subcutaneously and 400 mg orally have not been associated with side effects other than those mentioned.

In clinical studies volunteers have received 20 mg of sumatriptan by the intranasal route three times a day for a period of 4 days without significant adverse effects.

Treatment
If overdosage 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 sumatriptan.

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.

Clinical response begins 15 minutes following a 20mg dose given by intra-nasal administration.

Because of its route of administration Imigran nasal spray may be particularly suitable for patients who suffer with nausea and vomiting during an attack.

5.2 Pharmacokinetic properties

The pharmacokinetics of intra-nasal sumatriptan do not appear to be significantly affected by migraine attacks.

The kinetics in the older people have been insufficiently studied to justify a statement on possible differences in kinetics between older people and young volunteers.

Absorption:
Rapid. However relative to sub-cutaneous administration the mean bioavailability is about 16% following intranasal sumatriptan and about 14% following oral sumatriptan, partly due to pre-systemic metabolism.

Distribution:
Sumatriptan is rapidly and extensively distributed to tissues, but passage across the blood-brain barrier is limited. The mean volume of distribution is 170 litres.

Protein binding:
Plasma protein binding is low (14-21%).

Biotransformation:
Hepatic and extensive; approximately 80% of a dose is metabolised.
The major metabolite is an inactive indole acetic acid derivative. Minor metabolites have not been identified.

Half-life:
The elimination half-life is approximately 2 hours.

Onset of Action:
From 15 minutes.

Time to Peak Concentration:
Maximum plasma concentration occurs in 1-1.5 hours. The wide interindividual variability found in pharmacokinetic studies may be related to the appearance of multiple peaks in the concentration over time.

Peak Concentration:
After a 20mg intranasal dose, the mean maximum plasma concentration is 13ng/mL.

Time to peak effect:
The time to maximal effect is 2 hours.

Duration of action:
Return of migraine headache occurs within 24 to 48 hours in 19-41% of patients taking a 20mg intranasal dose who initially gained 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:
The mean total plasma clearance is approximately 1160ml/min and the mean renal plasma clearance is approximately 260ml/min. Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5HT_1$ or $5HT_2$ activity.

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

In studies carried out to test for local and ocular irritancy, following administration of sumatriptan nasal spray, there was no nasal irritancy seen in laboratory animals and no ocular irritancy observed when the spray was applied directly to the eyes of rabbits.

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

Potassium Dihydrogen Phosphate
Disodium Phosphate anhydrous
Sulphuric Acid
Sodium Hydroxide
Purified Water

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 in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

Imigran Nasal Spray is supplied in Type 1 glass vials sealed with chlorobutyl rubber stoppers and with an applicator. Each unit dose spray device containing 0.1 ml solution is presented in an individually sealed blister.

Packs contain 1, 2, 4, 6, 12, or 18 sprays.

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

PA1077/008/004

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10 DATE OF REVISION OF THE TEXT

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