Pharma code Ref. No. 1290

IMIGRAN™

Sumatriptan Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 50 or 100 mg of sumatriptan base as the succinate salt.

PHARMACEUTICAL FORM

IMIGRAN tablets 50 mg are pink, film coated, with "GXES3" engraved on one face and plain on the other face, or plain on one face and engraved "50" on the other.

IMIGRAN tablets 100 mg are white to off-white, film coated, with "GXET2" engraved on one face and plain on the other face, or plain on one face and engraved "100" on the other.

CLINICAL PARTICULARS

Indications

IMIGRAN tablets are indicated for the acute relief of migraine attacks with or without aura, including the acute treatment of migraine attacks associated with the menstrual period in women.

Dosage and Administration

IMIGRAN should not be used prophylactically. The recommended dose of *IMIGRAN* should not be exceeded.

It is advisable that sumatriptan 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.

Populations

- **Adults**

The recommended dose of oral *IMIGRAN* is a single 50 mg tablet. Some patients may require 100 mg.

If a patient does not respond to the first dose of *IMIGRAN*, a second dose should not be taken for the same attack. *IMIGRAN* tablets 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 two hours between doses and not more than 300 mg is taken in any 24-hour period.

The tablets should be swallowed whole with water.

- **Children and Adolescents (under 18 years of age)**

The efficacy of sumatriptan tablets in this population has not been demonstrated (*see Clinical Studies*).

- **Elderly (over 65 years of age)**

Experience of the use of sumatriptan tablets 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* in patients aged over 65 years is not recommended.

Contraindications

- Hypersensitivity to any component of the preparation.
- *IMIGRAN* should not be given to patients who have had myocardial infarction or have ischaemic heart disease (IHD), Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.
- *IMIGRAN* should not be administered to patients with a history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- The use of *IMIGRAN* in patients with uncontrolled hypertension is contraindicated.
- *IMIGRAN* should not be administered to patients with severe hepatic impairment.
- The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (*see Interactions*).
- Concurrent administration of monoamine oxidase inhibitors (MAOIs) and *IMIGRAN* is contraindicated. *IMIGRAN* must not be used within two weeks of discontinuation of therapy with MAOIs.

Warnings and Precautions

IMIGRAN should only be used where there is a clear diagnosis of migraine.

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

Before treating with *IMIGRAN*, 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 *IMIGRAN* use.

Following administration, *IMIGRAN* can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (*see Adverse Reactions*). Where such symptoms are thought to indicate IHD appropriate evaluation should be carried out.

IMIGRAN should not be given to patients in whom unrecognised cardiac disease is likely without a prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over 40 and patients with risk factors for coronary artery disease. However, these evaluations 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.

IMIGRAN 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.

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 re-uptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline re-uptake inhibitors (SNRIs).

If concomitant treatment with *IMIGRAN* 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 *IMIGRAN* is not recommended

IMIGRAN should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism or excretion of the drug, e.g. impaired hepatic (Child Pugh grade A or B; *see Pharmacokinetics – Special Patient Populations*) or renal function (*see Pharmacokinetics*).

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

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

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

Interactions

There is no evidence of interactions with propanolol, flunarizine, pizotifen or alcohol.

Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until six hours have elapsed following *IMIGRAN* administration.

An interaction may occur between *IMIGRAN* and MAOIs and concomitant administration is contraindicated (*see Contraindications*).

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*).

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 the 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.

Effects on Ability to Drive and Use Machines

Drowsiness may occur as a result of migraine or treatment with sumatriptan.

Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

Adverse Reactions

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 (≥1/10000 to <1/1000) and very rare (<1/10000) 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.

Respiratory, Thoracic and Mediastinal Disorders

Common: Dyspnoea.

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.

121910

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180 mm Measuring Bar

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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 Contraindications, Warnings and Precautions*).

Vascular disorders

Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Very rare: Ischaemic colitis.

Overdose

Symptoms and Signs

Doses in excess of 400 mg orally were not associated with side effects other than those mentioned.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

N02CC01.

Mechanism of Action

Pharmacotherapeutic group: Selective 5-HT_1 receptor agonists.

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5-HT_1D) receptor agonist with no effect at other 5-HT receptor (5-HT_{2-7}) subtypes. The vascular 5-HT_1D receptor is found predominantly in cranial blood vessels and mediates vasoconstriction.

In animals, sumatriptan selectively constricts the carotid arterial circulation, but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. In addition, experimental evidence suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions 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 minutes following a 20 mg dose given by intra-nasal administration and around 30 minutes following a 100 mg oral dose or 25 mg rectal dose.

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

IMIGRAN is effective in the acute treatment of migraine including menstrually-associated migraine.

Pharmacokinetics

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

Absorption

After oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After a 100 mg dose the mean maximum plasma concentration is 54 nanograms/mL.

Mean absolute oral bioavailability is 14% partly due to pre-systemic metabolism and partly due to incomplete absorption.

Distribution

Plasma protein binding is low (14 to 21%); the mean total volume of distribution is 170 litres.

Metabolism

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 5-HT_1 or 5-HT_2 activity. Minor metabolites have not been identified.

Elimination

The elimination half-life is approximately two hours. The mean total plasma clearance is approximately 1,160 mL/min and the mean renal plasma clearance is approximately 260 mL/min.

Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.

Special Patient Populations

- **Hepatic impairment**

Following oral administration, pre-systemic clearance is reduced in patients with hepatic impairment resulting in increased plasma levels of sumatriptan (*see Warnings and Precautions*).

Clinical Studies

A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan standard tablets in over 650 child and adolescent migraineurs aged 10 to 17 years. These studies failed to demonstrate a statistically significant difference in headache relief at two hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in children and adolescents aged 10 to17 years was similar to that reported from studies in the adult population.

Pre-Clinical Safety Data

Carcinogenesis, mutagenesis

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

Reproductive toxicology

In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man after a 100 mg oral dose were associated with a reduction in the success of insemination.

This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 150 times those in man by the oral route.

Pregnancy and lactation

No teratogenic effects have been seen in rats or rabbits, and sumatriptan had no effect on the post-natal development of rats.

When administered to pregnant rabbits throughout the period of organogenesis sumatriptan has occasionally caused embryolethality at doses that were sufficiently high to produce maternal toxicity.

PHARMACEUTICAL PARTICULARS

List of Excipients

50 mg

Lactose (monhydrate)
Lactose (anhydrous)
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Purified water

100 mg

Lactose (monhydrate)
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Purified water

Incompatibilities

None reported.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store *IMIGRAN* tablets above 30°C.

Nature and Contents of Container

IMIGRAN tablets 50 mg are packed in individual pockets in cold form foil/child-resistant lidding foil blister packs and placed in a cardboard carton.

IMIGRAN tablets 100 mg are packed in individual pockets in cold form foil/child-resistant lidding foil blister packs and placed in a cardboard carton.

Instructions for Use/Handling

None.

Not all presentations are available in every country.

Manufactured and Packed by:

GlaxoSmithKline Pharmaceuticals S.A.,

Poznan

Poland

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