NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IMIGRAN® sumatriptan succinate 50 mg and 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg or 100 mg of sumatriptan base, as the succinate salt, to be taken orally.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Tablets.

IMIGRAN 50 mg tablets: pink, film-coated, capsule shaped, biconvex tablets, engraved with ‘50’ on one side and plain on the other.

IMIGRAN 100 mg tablets: white or off-white film-coated, capsule shaped, biconvex tablets engraved with ‘100’ on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMIGRAN tablets are indicated for the acute relief of migraine attacks with or without aura in adults aged 18 to 65 years.

4.2 Dose and method of administration

Dose

Use in Adults

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

It is advisable that IMIGRAN 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.

The recommended adult dose of oral IMIGRAN is a 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 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.
Special Populations

Paediatric population

The efficacy of sumatriptan tablets in patients under 18 years of age has not been demonstrated.

Elderly population

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

Method of administration

The tablets should be swallowed whole with water.

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 (IHD), Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.

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

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

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

The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see section 4.5 Interaction with other medicines and other forms of interaction).

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

4.4 Special warnings and precautions for use

IMIGRAN tablets 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 Undesirable effects). Where such symptoms are thought to indicate ischaemic heart disease appropriate evaluation should be carried out.
Sumatriptan 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.

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.

There have been rare postmarketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability, 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 Interaction with other medicines and other forms of interaction).

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

Sumatriptan should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of the medicine, eg. impaired hepatic (Child Pugh grade A or B; see section 5.2 Pharmacokinetic properties – Special populations) or renal function (see section 5.2 Pharmacokinetic properties – Special populations).

Sumatriptan 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 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.

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.

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been reported with use of serotonergic agents such as SSRIs or triptans.

4.5 Interaction with other medicines and other forms of interaction

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 sumatriptan administration.
An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see section 4.3 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 (see section 4.4 Special warnings and precautions for use).

Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see section 4.4 Special warnings and precautions for use).

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 the general population.

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 which were sufficiently high to produce maternal toxicity.

Breast-feeding

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.

Fertility

No data are available.

4.7  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, eg. driving or operating machinery.

4.8  Undesirable effects

Tabulated list of 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 (≥1/10,000 to <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.

**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.

**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 and section 4.4 Special warnings and precautions for use).

**Vascular disorders**

Very rare: Hypotension, Raynaud’s phenomenon.

**Gastrointestinal Disorders**

Very rare: Ischaemic colitis.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: [https://nzphvc.otago.ac.nz/reporting](https://nzphvc.otago.ac.nz/reporting).

**4.9 Overdose**

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

If overdosage 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 sumatriptan.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective 5-HT\textsubscript{1} receptor agonists, ATC code: N02CC01.

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5HT\textsubscript{1}D) receptor agonist with no effect at other 5HT receptor (5HT\textsubscript{2}-5HT\textsubscript{7}) subtypes. The vascular 5HT\textsubscript{1}D 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.

Clinical response begins 10-15 minutes following a 6 mg subcutaneous injection, and around 30 minutes following a 100 mg oral dose.

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

5.2 Pharmacokinetic properties

The pharmacokinetics of oral 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 ng/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 (14-21\%); the mean total volume of distribution is 170 litres.
Biotransformation

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 5HT₁ or 5HT₂ activity. Minor metabolites have not been identified.

Elimination

The elimination half-life is approximately 2 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 populations

Hepatic impairment

Following oral administration, pre-systemic clearance is reduced in patients with hepatic impairment resulting in increased plasma levels of sumatriptan (see section 4.4 Special warnings and precautions for use).

5.4 Preclinical 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.

6. PHARMACEUTICAL PRECAUTIONS

6.1 List of excipients

IMIGRAN tablets contain the following excipients:

- lactose
- microcrystalline cellulose (460)
- croscarmellose sodium
- magnesium stearate (572).

IMIGRAN tablets 100 mg are coated with hypromellose (464) and Opadry White OY-S-7393.

IMIGRAN tablets 50 mg are coated with Opadry YS-1-1441-G.
IMIGRAN tablets do not contain gluten.

6.2 Incompatibilities

None reported.

6.3 Shelf Life

48 months

6.4 Special precautions for storage

IMIGRAN tablets should be stored below 30°C.

6.5 Nature and contents of container

IMIGRAN tablets are packed in child-resistant foil blister packs in cartons.

IMIGRAN 50 mg tablets 4 x 50 mg tablets
IMIGRAN 100 mg tablets 2 x 100 mg tablets

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINES SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
13 November 1997

10. DATE OF REVISION OF THE TEXT

4 August 2017

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