NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IMIGRAN injection 6 mg/0.5 mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 6 mg of sumatriptan base, as the succinate salt, in 0.5 mL.

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

3. PHARMACEUTICAL FORM

Subcutaneous solution for injection.

Pre-filled syringe containing a colourless to pale yellow, isotonic solution. The pre-filled syringe can only be used in conjunction with an autoinjector.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMIGRAN injection is indicated for the acute relief of migraine attacks with or without aura, and for the acute treatment of cluster headache in adults aged 18 years and over.

4.2 Dose and method of administration

Dose

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

It is recommended to start the treatment at the first sign of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. The efficacy of sumatriptan is independent of the duration of the attack when starting treatment. Administration during a migraine aura prior to other symptoms occurring may not prevent the development of a headache.

Adults (18 years and over)

Migraine

The recommended adult dose of IMIGRAN injection is a 6 mg subcutaneous injection.

If a patient does not respond to the first dose of IMIGRAN, a second dose should not be taken for the same attack. IMIGRAN injection 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 one hour between the two doses.

The maximum dose in 24 hours is two 6 mg injections (12 mg).

Cluster Headache

The recommended adult dose of IMIGRAN injection is a single 6 mg subcutaneous injection for each cluster attack.

The maximum dose in 24 hours is two 6 mg injections (12 mg) with a minimum interval of one hour between the two doses.

Children and Adolescents (under 18 years of age)

Sumatriptan injection has not been studied in adolescents or children.

Special populations

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

IMIGRAN injection should be injected subcutaneously using an autoinjector.

Patients should be advised to observe strictly the instruction leaflet for the IMIGRAN autoinjector, especially regarding the safe disposal of syringes and needles.

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 injection should only be used where there is a clear diagnosis of migraine or cluster headache.

Latex Allergy - The needle shield of the pre-filled syringe may contain dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

IMIGRAN injection should not be given intravenously.

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

Before treating with sumatriptin 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 disgnosis 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 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 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-HT_1 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 Patient Populations) or renal function (see section 5.2 Pharmacokinetic properties).

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

There are no data on the effects of sumatriptan on fertility in humans.

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)

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.

Injection:

The most common side effects associated with treatment with IMIGRAN administered subcutaneously are:

General Disorders and Administration Site Conditions

Very common:	Transient injection site pain.
	Injection site stinging/burning, swelling, erythema, bruising and bleeding have also been reported.

Although direct comparisons are not available, flushing, paraesthesia and sensations of heat, pressure, and heaviness may be more common after IMIGRAN injection.

Conversely, nausea, vomiting and fatigue appear to be less frequent with subcutaneous administration of IMIGRAN injection than with tablets.

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.

4.9 Overdose

There have been some reports of overdosage with IMIGRAN injection.

Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Doses up to 16 mg subcutaneously 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: Analgesics, selective 5-HT_1 receptor agonists; ATC code: N02CC01.

Mechanism of action

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

5.2 Pharmacokinetic Properties

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

Absorption

Following subcutaneous injection sumatriptan has a high mean bioavailability (96%) with peak serum concentrations occurring in 25 minutes. Average peak serum concentration after a 6 mg subcutaneous dose is 72 nanograms/mL.

Distribution

Plasma protein binding is low (14-21%); 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 $5HT_1$ or $5HT_2$ 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

The effect of moderate hepatic disease (Child Pugh grade B) on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls (see section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

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

In a rat fertility study oral doses of sumatriptan resulting in plasma levels approximately 150 times those seen in man after a 6mg subcutaneous 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 100 times those in man by the subcutaneous route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

IMIGRAN injection contains the following excipients:

- sodium chloride
- water for injections

IMIGRAN injection does not contain lactose, sucrose or gluten.

6.2 Incompatibilities

None reported.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

IMIGRAN injection should be stored below 30°C, protected from light.

6.5 Nature and contents of container

IMIGRAN injection is available as two prefilled syringes in a refill pack cartridge packed in a carton with a leaflet.

The Carry-Case containing the Autoinjector Pen is packed in a separate carton with patient instructions for using the Autoinjector.

6.6 Special precautions for disposal and other handling

Patients should be advised to pay strict attention to the instruction leaflet for IMIGRAN injection especially regarding the safe disposal of needles and syringes.

Needles and syringes may be hazardous and should be disposed of safely and hygienically.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland 1143
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: 11 April 1991

10. DATE OF REVISION OF THE TEXT

10 January 2018

Summary table of changes:

Section changed	**Summary of new information**
All	Data Sheet re-format
4.1	Added age range to indication
4.4	Addition of warning regarding latex
4.6	Added Fertility section
4.8	Added reporting of suspected adverse reactions information
4.9	Added information regarding advice on the management of overdose
5.1	Added Pharmacotherapeutic group and ATC code
6.6	Added information regarding disposal
9	Added date of first approval

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