

e-Banner	Project: CO-0029419	Document: PPC-0024224	Version: 3
	Site Code: 6200000052459	Operator: KA173176	Date/Time Created: 25.Jun.2020 18:40 GMT+1

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Version: 1		
Harmony AMS Artwork Information Panel		
Manufacturing Site Number: 6200000052459		
Manufacturing Site(s): GSK_BARNARD CASTLE_UNITED KINGDOM		
Product Market Trade Name: IMIGRAN		
Approving Market(s): MARKET GROUP-Gulf and Near East		
Print Process: N/A		
Colour Standard Reference: N/A		
Technical Drawing (Do NOT include version number): JMF301		
Material Spec. (Do NOT include version number): N/A		
Material Type: N/A	N/A	
Total Colours & Varnishes: 1		
BLACK		
Total Special Finishes: 0		
Body Text Size: 8.0pt		
Smallest Text Size: 8.0pt		
Leading: 8.5pt		
Horizontal Scale: 100%		
Microtext: N		
Additional Info (1): N/A		
Additional Info (2): N/A		
Additional Info (3): N/A		

200 mm Measuring Bar
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IMPORTANT

GSK LOC is responsible to approve the change documentation, artwork brief and final artwork, ensuring that it is accurate, consistent and complete.

GSK SDC is responsible for site technical requirements and pre-press suitability.

GSK Market is responsible to advise SDC when changes required impact the following:

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NOTE TO MARKET

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Imigran Injection sumatriptan succinate



QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 6 mg of sumatriptan base, as the succinate salt, in an isotonic solution of 0.5 ml.
For a full list of excipients, see section "List of excipients".

PHARMACEUTICAL FORM

Pre-filled syringes for use in conjunction with an auto injector for subcutaneous injection.

CLINICAL PARTICULARS

Therapeutic indications

Subcutaneous Injection is indicated for the acute relief of migraine attacks, with or without aura, and for the acute treatment of cluster headache. Imigran should only be used where there is a clear diagnosis of migraine or cluster headache.

Posology and method of administration

Imigran should not be used prophylactically. The recommended dose of Imigran 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. It is equally effective at whatever stage of the attack it is administered. 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. Imigran Injection should be injected subcutaneously using an auto-injector. Patients should be advised to observe strictly the instruction leaflet for the Imigran auto-injector especially regarding the safe disposal of syringes and needles.

Migraine:

Adult: The recommended adult dose of Imigran is a single 6 mg subcutaneous injection. If a patient does not respond to the first dose of sumatriptan, 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. Sumatriptan 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 1 hour between the two doses. The maximum dose in 24 hours is two 6 mg injections (12 mg).
Imigran is recommended as monotherapy for the acute treatment of migraine and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section "Contraindications").

Cluster headache:

Adult: The recommended adult dose is a single 6mg 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 is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

Older people (over 65):

Experience of the use of Imigran 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.

Contraindications

Hypersensitivity to sumatriptan or to any of the excipients listed in section "List of excipients".

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 contraindicated.

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine₁ (5-HT₁) receptor agonist with sumatriptan is contraindicated. (see section "Interaction with other medicinal products and other forms of Interaction").

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.

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

Special warnings and precautions for use

Warnings: Imigran should only be used where there is a clear diagnosis of migraine or cluster headache. Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine. 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 because of its potential to cause vasospasm. The vasospasm may result in arrhythmias, ischaemic ECG changes or myocardial infarction. 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 "Undesirable effects"). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan should be given and appropriate evaluation should be carried out.

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 "Contraindications"). 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.

If the patient experiences symptoms which are severe or persistent or are consistent with angina, further doses should not be taken until appropriate investigations have been carried out to check for the possibility of ischaemic changes.

Sumatriptan should be administered 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 "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 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 "Interaction with other medicinal products and other forms of Interaction").

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 "Pharmacokinetic properties") or renal function (see section "Pharmacokinetic properties"). 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 "Undesirable effects").

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.

Interaction with other medicinal products and other forms of Interaction

Studies in healthy subjects show that Imigran does not interact 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 contraindicated (see section "Contraindications").

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 types 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 "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 section "Special warnings and precautions for use").

Fertility, pregnancy and lactation

Pregnancy

Post-marketing data from the use of sumatriptan during the first trimester 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 effects or harmful effects on peri- and postnatal development. However, embryofetal viability might be affected in the rabbit (see section "Preclinical safety data").

Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

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, during which time any breast milk expressed should be discarded.

Effect 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 treatment with sumatriptan. This may influence the ability to drive and to operate machinery.

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 (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data). Some of the symptoms reported as undesirable effects may be associated symptoms of migraine.

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 it is unclear if this is related to sumatriptan or the underlying condition.

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.

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.

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).

Although direct comparisons are not available, flushing, paraesthesia and sensations of heat, pressure, and heaviness may be more common after sumatriptan injection. Conversely, nausea, vomiting and fatigue appear to be less frequent with subcutaneous administration of sumatriptan injection than with tablets.

Investigations

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

6200000052459


Pharma code Ref: No. 4927

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BACK

X1

Version: 1		
Harmony AMS		
Artwork Information Panel		
Manufacturing Site Number: 6200000052459		
Manufacturing Site(s): GSK_BARNARD CASTLE_UNITED KINGDOM		
Product Market Trade Name: IMIGRAN		
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Print Process: N/A		
Colour Standard Reference: N/A		
Technical Drawing (Do NOT include version number): JMF301		
Material Spec. (Do NOT include version number): N/A		
Material Type: N/A	N/A	
Total Colours & Varnishes: 1		
BLACK		
Total Special Finishes: 0		
Body Text Size: 8.0pt		
Smallest Text Size: 8.0pt		
Leading: 8.5pt		
Horizontal Scale: 100%		
Microtext: N		
Additional Info (1): N/A		
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Post-Marketing Data**Immune System Disorders**

Not known: Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis.

Nervous System Disorders

Not known: 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

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 "Contraindication" & "Special warnings and precautions for use").

Vascular Disorders

Not known: Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Not known: Ischaemic colitis. Diarrhoea.

Musculoskeletal, Connective Tissue and Bone Disorders

Not known: Neck stiffness. Arthralgia.

Psychiatric disorders

Not known: Anxiety.

Skin and subcutaneous tissue disorders

Not known: Hyperhidrosis.

Reporting of suspected adverse reactionsTo report Product Complaint/s or Adverse Event/s associated with the use of GSK product/s, please contact us via: gulf.safety@gsk.com.**Overdose**

There have been some reports of overdose with Imigran Injection. Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Doses in excess of 16 mg subcutaneously were not associated with side effects other than those mentioned. If overdose with Imigran 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 Imigran.

PHARMACOLOGICAL PROPERTIES**Pharmacodynamic properties**Pharmacotherapeutic group: Analgesics: Selective 5-HT₁ receptor agonists.
ATC Code: N02CC01Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine (5-HT_{1D}) receptor agonist with no effect on other 5-HT receptor (5-HT₂-5-HT₇) 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 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.

Sumatriptan remains effective in treating menstrual migraine i.e. migraine without aura that occurs between 3 days prior and up to 5 days post onset of menstruation. Sumatriptan should be taken as soon as possible in an attack.

Clinical response begins 10 to 15 minutes following a 6mg subcutaneous injection.

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

Pharmacokinetic properties

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 ng/ml. The elimination phase half-life is approximately two hours. Plasma protein binding is low (14 to 21%), mean volume of distribution is 170 litres. Mean total plasma clearance is approximately 1160 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.

The major metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine where it is present as a free acid and the glucuronide conjugate. It has no known 5-HT₁ or 5-HT₂ activity. Minor metabolites have not been identified.

In a pilot study, no significant differences were found in the pharmacokinetic parameters between older people and young healthy volunteers.

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 "Special warnings and precautions for use").

Preclinical safety dataSumatriptan 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 6 mg 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.

In rabbits embryolethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

PHARMACEUTICAL PARTICULARS**List of excipients**Sodium Chloride
Water for Injection**Incompatibilities**

None Reported

Shelf life

Two years when stored below 30°C and protected from light.

Special precautions for storage

Imigran Injection should be stored below 30°C and protected from light.

Nature and contents of container

Treatment pack: 2 pre-filled syringes (in cases) plus an auto-injector, in a plastic tray within a carton.

Refill pack: 2 pre-filled syringes (in cases) in a carton or 6 pre-filled syringes (ie three cases each containing 2 pre-filled syringes).

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.

Revision Date: January 2020

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- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

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