IMITREX INJECTION
SUMMARY OF PRODUCT CHARACTERISTICS

1. Trade Name of the Medicinal Product

Imitrex Injection

2. 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 6.1

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

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

4.2 Posology and method of administration

Imitrex Injection should not be used prophylactically. The recommended dose of Imitrex 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.

Imitrex Injection should be injected subcutaneously using an auto-injector. Patients should be advised to observe strictly the instruction leaflet for the Imitrex auto-injector especially regarding the safe disposal of syringes and needles.

Migraine:

Adult*:* The recommended adult dose of Imitrex is a single 6mg 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 6mg injections (12mg).

Imitrex 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 4.3).

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 6mg injections (12mg) 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 Imitrex Injection 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.

4.3 Contraindications

Hypersensitivity to sumatriptan or to any of the excipients listed in 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 contraindicated.

The concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist with sumatriptan is contraindicated. (see section 4.5)

Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.

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

4.4 Special warnings and precautions for use

Warnings: Imitrex 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 opthalmoplegic 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.

Imitrex 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 4.8). 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 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.

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 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 a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs) and triptan with tricyclic antidepressants (TCAs).

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.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT1 agonists have not been clearly established.

This medicine contains less than 1 mmol sodium (23 mg) per syringe, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Studies in healthy subjects show that Imitrex 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 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 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 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) and triptan with tricyclic antidepressants (TCAs).

4.6. 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, embryofoetal 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.

Breast-feeding

Sumatriptan is excreted into breast milk, with average relative infant doses of < 4% following administration of a single dose of sumatriptan. Infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment, during which time any breast milk expressed should be discarded.

There have been reports of breast pain and/or nipple pain following sumatriptan intake in breastfeeding women (see section 4.8). The pain was usually transient and disappeared in 3 to 12 hours.

4.7 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.

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 (≥1/10000 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

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 4.3 and 4.4).

Vascular Disorders

Not known:	Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders

Not known:	Ischaemic colitis, diarrhoea, dysphagia.

Musculoskeletal, Connective Tissue and Bone Disorders

Not known:	Neck stiffness. Arthralgia.

Reproductive system and breast disorders

Rare:	Breast pain.

General Disorders and Administration Site Conditions

Not known:	Pain trauma activated, pain inflammation activated.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.
Additionally, you should also report to GSK Israel (il.safety@gsk.com)

4.9 Overdose

There have been some reports of overdose with Imitrex 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 Imitrex 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 Imitrex.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics: Selective 5-HT_1 receptor agonists. ATC Code: N02CC01

Sumatriptan 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-HT_2-5-HT_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 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 Imitrex Injection may be particularly suitable for patients who suffer with nausea and vomiting during an attack.

5.2 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-HT_1 or 5-HT_2 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 4.4).

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Water for Injection

6.2 Incompatibilities

None Reported

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging.

6.4 Special precautions for storage

Do not store above 30°C.
Imitrex Injection should be protected from light.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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

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

7. Manufacturer

Glaxo Operations (UK) Limited, Barnard Castle, UK.

8. License holder

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. Licence Number

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