Imitrex Nasal Spray 20 mg

1 NAME OF THE MEDICINAL PRODUCT

Imitrex Nasal Spray 20 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Imitrex Nasal Spray 20 mg: Unit dose spray device for intranasal administration. The device delivers 20 mg of sumatriptan in 0.1 mL of an aqueous buffered solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal Spray, solution.

Clear pale yellow to dark yellow liquid, in glass vials in a single dose nasal spray device.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Imitrex Nasal Spray is indicated for the acute treatment of migraine attacks with or without aura.

4.2 Posology and method of administration

Imitrex Nasal Spray should not be used prophylactically.

The recommended dose of Imitrex Nasal Spary should not be exceeded.

Imitrex Nasal Spray is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

It is advisable that Imitrex Nasal Spray 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.

Adults (18 years of age and over)

The optimal dose of Imitrex Nasal Spray is 20 mg for administration into one nostril.

If a patient does not respond to the first dose of Imitrex Nasal Spray, 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. Imitrex Nasal Spray 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 following 24 hours, provided that there is a minimum interval of 2 hours between the two doses.

No more than two doses of 20 mg Nasal Spray should be taken in any 24-hour period.

Children (under 18 years of age)

The use of Imitrex Nasal Spray 20 mg is not recommended in patients under the age of 18 years.

Elderly (over 65)

There is no experience of the use of Imitrex Nasal Spray in patients over 65. The pharmacokinetics in elderly patients have not been sufficiently studied. Therefore the use of sumatriptan is not recommended until further data are available.

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 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 is contraindicated (see section 4.5).

Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated.

Imitrex Nasal Spray must not be used within 2 weeks of discontinuation of therapy with monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Imitrex Nasal Spray 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). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan should be given and an 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 and in adolescents (see section 4.8).

Sumatriptan should be given with caution in 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 that may affect significantly the absorption, metabolism, or excretion of the drug, e.g. impaired hepatic (mild to

moderate impairment (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.

4.5 Interaction with other medicinal products and other forms of interaction

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

There are limited data on an interaction with preparations containing ergotamine or another triptan/5-HT_1 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-HT_1 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-HT_1 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-HT_1 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 and triptan with tricyclic antidepressants (TCAs) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Post-marketing data on the use of sumatriptan during the first trimester of pregnancy 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, embryo-foetal 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 secreted 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 breast-feeding women (see section 4.8). The pain was usually transient and disappeared in 3 to 12 hours.

4.7 Effects 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.

Immune system disorders

Not known:	Hypersensitivity reactions ranging from cutaneous hypersensitivity (such as urticaria) to anaphylaxis.

Nervous system disorders

Very common:	Dysgeusia/unpleasant taste.
Common:	Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia.
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

Common:	Transient increases in blood pressure arising soon after treatment. Flushing.
Not known:	Hypotension, Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders

Common:	Following administration of sumatriptan nasal spray mild, transient irritation or burning sensation in the nose or throat or epistaxis have been reported. 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.
Not known:	Ischaemic colitis, diarrhoea, dysphagia.

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.
Not known:	Neck stiffness.
	Arthralgia

Reproductive system and breast disorders

Rare:	Breast pain

General disorders and administration site conditions

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).
Not known:	Pain trauma activated, pain inflammation activated.

Investigations

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

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

Single doses of sumatriptan up to 40 mg intranasally, in excess of 16 mg subcutaneously and 400 mg orally have not been associated with side effects other than those mentioned.

In clinical studies volunteers have received 20 mg of sumatriptan by the intranasal route three times a day for a period of 4 days without significant adverse effects.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective 5-HT1 receptor agonists, ATC code: N02CC01.

Sumatriptan is a selective vascular 5-hydroxytryptamine-1-(5-HT1d) receptor agonist with no effect on other 5-HT receptor (5-HT2–5-HT7) subtypes. The vascular 5-HT1d 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, evidence from animal studies suggests that sumatriptan inhibits trigeminal nerve activity. Both cranial vasoconstriction and inhibition of trigeminal nerve activity may contribute to the anti-migraine action of sumatriptan in humans.

Clinical response begins 15 minutes following a 20 mg dose given by intranasal administration.

Because of its route of administration, Imitrex Nasal Spray may be particularly suitable for patients who suffer nausea and vomiting during a migraine attack.

The magnitude of treatment effect is smaller in adolescents compared with adults.

5.2 Pharmacokinetic properties

After intranasal administration, sumatriptan is rapidly absorbed, median times to maximum plasma concentrations being 1.5 (range: 0.25-3) hours in adults and 2 (range: 0.5-3) hours in adolescents. After a 20 mg dose, the mean maximum concentration is 13ng/mL. Mean intranasal bioavailability, relative to subcutaneous administration is about 16%, partly due to pre-systemic metabolism.

Plasma protein binding is low (14–21%) and the mean volume of distribution is 170L. The elimination half-life is approximately 2 hours. The mean total plasma clearance is approximately 1160mL/min and the mean renal plasma clearance is approximately 260mL/min.

A pharmacokinetic study in adolescent subjects (12–17 years) indicated that the mean maximum plasma concentration was 13.9ng/mL and mean elimination half-life was approximately 2 hours following a 20 mg intranasal dose. Population pharmacokinetic modelling indicated that clearance and volume of distribution both increase with body size in the adolescent population resulting in higher exposure in lower bodyweight adolescents.

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 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. The pharmacokinetic profile of intranasal sumatriptan does not appear to be significantly affected by migraine attacks.

Special Patient Populations

Elderly (over 65)

The kinetics in the elderly have been insufficiently studied to justify a statement on possible differences in kinetics between elderly and young volunteers.

Hepatic impairment

Sumatriptan pharmacokinetics after an oral dose (50 mg) and a subcutaneous dose (6 mg) were studied in 8 patients with mild to moderate hepatic impairment matched for sex, age, and weight with 8 healthy subjects. Following an oral dose, sumatriptan plasma exposure (AUC and Cmax) almost doubled (increased approximately 80%) in patients with mild to moderate hepatic impairment compared to the control subjects with normal hepatic function. There was no difference between the patients with hepatic impairment and control subjects after the s.c. dose. This indicates that mild to moderate hepatic impairment reduces presystemic clearance and increases the bioavailability and exposure to sumatriptan compared to healthy subjects. Following oral administration, pre-systemic clearance is reduced in patients with mild to moderate hepatic impairment and plasma exposure, measured by Cmax and AUC, almost doubled. Since a portion of the nasal spray dose is swallowed, patients with mild to moderate hepatic impairment could also have higher exposures, but to a lesser extent than observed after oral dosing. (see Section 4.4, Warnings and Precautions).
The pharmacokinetics of sumatriptan in patients with severe hepatic impairment have not been studied (see Section 4.3 Contraindications and Section 4.4 Warnings and Precautions).

5.3 Preclinical safety data

In non-clinical studies carried out to test for local and ocular irritancy, following administration of sumatriptan nasal spray, there was no nasal irritancy seen in laboratory animals and no ocular irritancy observed when the spray was applied directly to the eyes of rabbits.

Experimental studies of acute and chronic toxicity showed no evidence of toxic effects within the human therapeutic dose range. In a rat fertility study a reduction in success of insemination was seen at exposures sufficiently in excess of the maximum human exposure. In rabbits, embryo-lethality without marked teratogenic defects was seen.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphuric Acid

Potassium Dihydrogen Phosphate

Dibasic Sodium Phosphate anhydrous

Sodium Hydroxide

Purified Water.

6.2 Incompatibilities

Not applicable

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. Do not freeze.

Imitrex Nasal Spray should be kept in the sealed blister, preferably in the box, to protect from light.

6.5 Nature and contents of container

The container consists of a type I Ph.Eur. glass vial with rubber stopper and applicator.

Imitrex 20 mg Nasal Spray: unit dose spray device containing 0.1mL solution.

Pack contains 2 sprays.

6.6 Special precautions for disposal

No special requirements.

7. Manufacturer

GlaxoSmithKline Manufacturing S.p.A., Verona, Italy.

8. License Holder and Importer

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

9. License Number

113-98-29573

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