

## **DATA SHEET**

### **NAME OF MEDICINE**

ZOMIG NASAL SPRAY  
Zolmitriptan 5 mg

### **PRESENTATION**

ZOMIG NASAL SPRAY is an aqueous solution containing 50 mg/mL zolmitriptan, buffered to pH 5.0. The device delivers a unit dose of 5 mg and is intended for a single use only.

### **USES**

#### **ACTIONS**

In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant 5HT<sub>1B</sub> and 5HT<sub>1D</sub> receptor subtypes. Zolmitriptan is a high affinity 5HT<sub>1B/1D</sub> receptor agonist with modest affinity for 5HT<sub>1A</sub> receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5HT<sub>2</sub>, 5HT<sub>3</sub>, 5HT<sub>4</sub>, alpha<sub>1</sub>, alpha<sub>2</sub>, or beta<sub>1</sub>, adrenergic; H<sub>1</sub>, H<sub>2</sub>, histaminic; muscarinic; dopaminergic<sub>1</sub>, or dopaminergic<sub>2</sub> receptors.

It has been demonstrated that the pain sensitive structures of the cranial cavity in humans are the blood vessels and the vasculature of the dura mater.

These tissues are innervated by trigeminal afferent fibres. In animal models the administration of zolmitriptan, with its agonist activity on the vascular 5HT<sub>1</sub> receptors causes vasoconstriction associated with an inhibition of the release of calcitonin gene related peptide (CGRP), Vasoactive Intestinal Peptide (VIP) and substance P. These two events, vasoconstriction and inhibition of neuropeptide release are thought to cause relief from the migraine attack, and associated nausea and vomiting, photophobia and phonophobia within 15 minutes of administration of ZOMIG NASAL SPRAY.

In addition to these peripheral actions, zolmitriptan has action on the central nervous system allowing access to both the peripheral and migraine centres in the brain stem which may explain the consistent effect over a series of attacks in a single patient. Vasodilatation is achieved with the activation of a reflex pathway mediated by trigeminal orthodromic fibres and parasympathetic innervation of the cerebral circulation via the release of VIP as a main effector transmitter. Zolmitriptan blocks this reflex pathway and the release of VIP.

In a clinical trial with ZOMIG NASAL SPRAY including just over 1300 migraine patients treating up to 3 migraine attacks the onset of efficacy is apparent from 15 minutes. At 2 hours post dose ZOMIG NASAL SPRAY 5 mg demonstrated headache response (from severe/moderate to mild/none) in 70% and pain free response in 36% of attacks compared to 31% and 8% respectively for placebo.

## PHARMACOKINETICS

Zolmitriptan is rapidly absorbed following intranasal administration with detectable levels in the plasma within 5 minutes of dosing. A proportion of the dose is directly absorbed in the nasopharynx. Forty percent of  $C_{max}$  is achieved within 15 minutes. Plasma concentrations are sustained for 4 to 6 hours. Elimination of zolmitriptan and the active metabolite 183C91 after oral and intranasal delivery were similar; the mean elimination half-life ( $t_{1/2}$ ) for both zolmitriptan and 183C91 are approximately 3 hours. The bioavailability of intranasal zolmitriptan relative to oral administration is 102%.

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. There are three major metabolites: the indole acetic acid, (the major metabolite in plasma and urine), the N-oxide and N-desmethyl analogues. The N-desmethylated metabolite (183C91) is active whilst the others are not. Plasma concentrations of 183C91 are approximately half those of the parent drug, hence it would therefore be expected to contribute to the therapeutic action of zolmitriptan. Over 60% of a single oral dose is excreted in the urine (mainly as the indoleacetic acid metabolite) and about 30% in faeces mainly as unchanged parent compound.

A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and  $C_{max}$  were increased by 94% and 50% respectively in patients with moderate liver disease and by 226% and 47% in patients with severe liver disease compared with healthy volunteers. Exposure to the metabolites, including the active metabolite, was decreased. For the 183C91 metabolite, AUC and  $C_{max}$  were reduced by 33% and 44% in patients with moderate liver disease and by 82% and 90% in patients with severe liver disease.

The plasma half-life ( $t_{1/2}$ ) of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding  $t_{1/2}$  values for the 183C91 metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively.

Following intravenous administration, the mean total plasma clearance is approximately 10 mL/min/kg, of which one third is renal clearance.

Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. The volume of distribution following IV administration is 2.4 L/kg. Plasma protein binding is low (approximately 25%). The mean elimination half-life of zolmitriptan is 2.5 to 3 hours. The half-lives of its metabolites are similar, suggesting their elimination is formation-rate limited.

Renal clearance of zolmitriptan and its metabolites is reduced (7 to 8 fold) in patients with moderate to severe renal impairment compared to healthy subjects, although the AUC of the parent compound and the active metabolite were only slightly higher (16 and 35% respectively) with a 1 hour increase in half-life to 3 to 3.5 hours. These parameters are within the ranges seen in healthy volunteers.

In a small group of healthy individuals, there was no pharmacokinetic interaction with ergotamine. Concomitant administration of zolmitriptan with ergotamine/caffeine was well tolerated and did not result in any increase in adverse events or blood pressure changes as compared to zolmitriptan alone (see INTERACTIONS regarding ergotamine use).

Selegiline, a MAO-B inhibitor, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), had no effect on the pharmacokinetic parameters of zolmitriptan.

## **INDICATIONS**

ZOMIG NASAL SPRAY is indicated for the acute treatment of migraine with or without aura.

ZOMIG NASAL SPRAY should only be used where there is a clear diagnosis of migraine.

## **DOSAGE AND ADMINISTRATION**

### **ADULTS (18-65 YEARS OF AGE)**

For correct administration of ZOMIG NASAL SPRAY, see package insert for instructions.

The recommended dose of ZOMIG NASAL SPRAY to treat a migraine attack is 5 mg administered as a single dose into one nostril.

ZOMIG NASAL SPRAY provides a particularly rapid onset of relief of migraine with significant efficacy apparent within 15 minutes of dosing.

If there is no response to the first dose, a second dose should not be taken for the same attack.

The effect of ZOMIG NASAL SPRAY is unaffected by co-administered nasal sympathomimetic decongestants.

### **USE IN CHILDREN AND ADOLESCENTS (UNDER 18 YEARS OF AGE)**

Not to be used in children or adolescents under 18 years of age. Efficacy has not been established in children.

### **USE IN THE ELDERLY (OVER 65 YEARS OF AGE)**

Not to be used in those over 65 years of age.

## **CONTRAINDICATIONS**

- ZOMIG NASAL SPRAY must not be used prophylactically
- Known hypersensitivity to any component of the product or to sulphonamides
- Known hypertension
- Previous myocardial infarction
- Ischaemic heart disease eg angina
- Peripheral vascular disease
- Coronary vasospasm/Prinzmetal's angina
- Cardiac arrhythmias (including Wolff-Parkinson-White syndrome)
- Hepatic or renal impairment
- Epilepsy or history of seizures
- Atypical migraine (including hemiplegic, basilar or ophthalmoplegic migraine)
- A history of cerebrovascular accident or transient ischaemic attack

- Concomitant administration with ergotamine, ergotamine derivatives, other triptans, monoamine oxidase inhibitors (see INTERACTIONS).

## **WARNINGS AND PRECAUTIONS**

ZOMIG NASAL SPRAY should only be used where a clear diagnosis of migraine has been established by a doctor or pharmacist. For pharmacy supply, patients should have an established pattern of migraine (a history of five or more migraine attacks occurring over a period of at least 1 year).

The recommended dose of ZOMIG NASAL SPRAY should not be exceeded.

Migraineurs whose typical headaches persist for longer than 24 hours should seek advice from their doctor.

Migraineurs in whom the pattern of symptoms has changed, or whose attacks have become more frequent, more persistent, or more severe, or who do not recover completely between attacks, should seek advice from their doctor.

Patients whose migraine symptoms appear for the first time after age 50 should seek advice from their doctor as there may be a more serious underlying cause.

Migraineurs who experience four or more migraine attacks per month should be referred to a doctor for ongoing management.

Migraineurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with 5HT<sub>1B/1D</sub> receptor agonists.

As with other 5HT<sub>1B/1D</sub> agonists, atypical sensations over the precordium (see ADVERSE EFFECTS) have been reported after the administration of zolmitriptan. Where such symptoms are thought to indicate ischaemic heart disease, no further doses of zolmitriptan should be given and appropriate evaluation carried out.

As with other 5HT<sub>1B/1D</sub> agonists transient increases in systemic blood pressure have been reported in patients with and without a history of hypertension; very rarely these increases in blood pressure have been associated with significant clinical events.

As with other 5HT<sub>1B/1D</sub> agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

Serotonin Syndrome has been reported with combined use of triptans, and Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition, and it may include signs and symptoms such as: mental status changes (e.g. agitation, hallucinations, coma), autonomic instability, (e.g. tachycardia, labile blood-pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, in-coordination), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). If concomitant treatment with ZOMIG NASAL SPRAY and an SSRI or SNRI is considered appropriate, patients should be advised to see their doctor if they develop symptoms of Serotonin Syndrome.

Following administration, triptans can be associated with transient symptoms including chest pain and tightness that may be intense and involve the throat (see ADVERSE EFFECTS). Typically, such symptoms develop within 30 minutes of treatment and last for less than 2

hours. Where such symptoms are thought to indicate ischaemic heart disease, medical evaluation should be obtained immediately.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (*Hypericum perforatum*).

#### **USE IN PREGNANCY AND LACTATION**

ZOMIG NASAL SPRAY should not be used in pregnancy or lactation unless on the advice of a doctor.

#### **EFFECT ON ABILITY TO DRIVE OR OPERATE MACHINERY**

ZOMIG NASAL SPRAY is unlikely to result in an impairment of the ability of patients to drive or operate machinery. However it should be taken into account that somnolence may occur.

#### **ADVERSE EFFECTS**

ZOMIG NASAL SPRAY is well tolerated. Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment.

Possible adverse reactions tend to occur within four hours.

The following definitions apply to the incidence of undesirable effects:

Very common ( $\approx 1/10$ ); common ( $\approx 1/100$  to  $<1/10$ ); uncommon ( $\approx 1/1,000$  to  $<1/100$ ); rare ( $\approx 1/10,000$  to  $<1/1,000$ ); very rare ( $<1/10,000$ ).

The following undesirable effects have been reported following administration of zolmitriptan:

Table 1 - Table of Adverse Drug Reactions

<b>System Organ Class</b>	<b>Frequency</b>	<b>Undesirable Effect</b>
Immune system disorders	Rare	Anaphylaxis/Anaphylactoid reactions Hypersensitivity reactions
Nervous system disorders	Very Common	Taste disturbance
	Common	Abnormalities or disturbances of sensation Dizziness Headache Hyperaesthesia Paraesthesia Somnolence Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Angina pectoris Coronary vasospasm Myocardial infarction
Vascular disorders	Uncommon	Transient increases in systemic blood pressure
Respiratory system disorders	Common	Epistaxis Discomfort of nasal cavity
Gastrointestinal disorders	Common	Abdominal pain Dry mouth Nausea Vomiting
	Very rare	Bloody diarrhoea Gastrointestinal infarction or necrosis Gastrointestinal ischaemic events Ischaemic colitis Splenic infarction
Skin and subcutaneous tissue disorders	Rare	Angioedema Urticaria
Musculoskeletal and connective tissue disorders	Common	Muscle weakness Myalgia
Renal and urinary disorders	Uncommon	Polyuria Increased urinary frequency
	Very rare	Urinary urgency
General disorders	Common	Asthenia Heaviness, tightness, pain or pressure in throat, neck, limbs or chest

## **INTERACTIONS**

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, 24 hours should elapse between the use of ergotamine containing or ergot-type medications (like dihydroergotamine or methysergide) and zolmitriptan. Conversely it is advised to wait at least 6 hours following use of ZOMIG NASAL SPRAY before administering an ergotamine containing preparation.

Concomitant administration of other 5HT<sub>1D/1B</sub> agonists within 12 hours of ZOMIG NASAL SPRAY treatment, should be avoided (see CONTRAINDICATIONS).

Cases of life threatening Serotonin Syndrome have been reported during combined use of triptans, and Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, sertraline) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (e.g. venlafaxine, duloxetine) (See WARNINGS AND PRECAUTIONS).

The absorption and pharmacokinetics of ZOMIG NASAL SPRAY are unaltered by prior nasal administration of the sympathomimetic vasoconstrictor, xylometazoline.

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Do not use ZOMIG NASAL SPRAY within 2 weeks of discontinuation of therapy with MAOIs.

Following the administration of cimetidine, a general P450 inhibitor, the half-life of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition, the half-life and AUC of the active, N-desmethylated, metabolite (183C91) were doubled. A maximum dose of 5 mg ZOMIG in 24 hours is recommended in patients taking cimetidine. Based on the overall interaction profile, an interaction with inhibitors of the cytochrome P450 isoenzyme CYP1A2 cannot be excluded. Therefore, the same dosage reduction is recommended with compounds of this type, such as fluvoxamine and the quinolone antibiotics (e.g. ciprofloxacin). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (*Hypericum perforatum*).

## **OVERDOSAGE**

Volunteers receiving single oral doses of 50 mg commonly experienced sedation.

The elimination half-life of zolmitriptan tablets is approximately 3 hours, (see PHARMACOKINETICS) and therefore monitoring of patients after overdose should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect haemodialysis or peritoneal dialysis has on serum concentrations of zolmitriptan.

## **PHARMACEUTICAL PRECAUTIONS**

### **SHELF-LIFE AND STORAGE CONDITIONS**

#### **Nasal Spray**

2 years. Store below 25°C

### **INSTRUCTIONS FOR USE / HANDLING**

#### **Nasal Spray**

The protective cover must not be removed until immediately before use. Please consult separate instruction leaflet.

## **MEDICINE CLASSIFICATION**

Restricted Medicine

## **PACKAGE QUANTITIES**

Two pre-filled nasal spray device per carton.

## **FURTHER INFORMATION**

### **PRE-CLINICAL SAFETY DATA**

An oral teratology study of zolmitriptan has been conducted. At the maximum tolerated doses of zolmitriptan , 1200mg/kg/day and 30 mg/kg/day in rats and rabbits, respectively, no signs of teratogenicity were apparent.

A number of genotoxicity tests have been performed. It was concluded that zolmitriptan is not likely to pose any genetic risk in humans.

Carcinogenicity studies in rats and mice were conducted at the highest feasible doses and gave no suggestion of tumourigenicity.

Reproductive studies in male and female rats, at dose levels limited by toxicity, revealed no effect on fertility.

### **EXCIPIENTS**

- citric acid
- disodium phosphate
- purified water

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