SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 2.5 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mg orodispersible tablet contains 2.5 mg of zolmitriptan.

Excipient with known effect:

Each 2.5 mg orodispersible tablet contains 0.250mg aspartame (E951).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

Zolmitriptan 2.5 mg orodispersible tablets are white to off-white round flat tablets of 5.5 mm diameter, debossed with ‘2.5’on one side, having a characteristic flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zolmitriptan 2.5 mg orodispersible tablets is indicated for the acute treatment of migraine headache with or without aura.

4 CLINICAL PARTICULARS

4.2 Posology and method of administration

Posology

The recommended dose of zolmitriptan to treat a migraine attack is 2.5mg.

If symptoms of migraine persist or recur within 24 hours, a second dose of zolmitriptan has been shown to be effective. If a second dose is required, it should not be taken within 2 hours of the initial dose.

If a patient does not achieve satisfactory relief with 2.5 mg doses, subsequent attacks can be treated with5 mg doses of zolmitriptan could be considered.

Zolmitriptan is equally effective whenever the tablets are taken during a migraine attack; although it is advisable that zolmitriptan is taken as early as possible after the onset of migraine headache.

In the event of recurrent attacks, it is recommended that the total intake of zolmitriptan in a 24-hour period should not exceed 10 mg.

Zolmitriptan is not indicated for prophylaxis of migraine.

Elderly

The safety and efficacy of zolmitriptan in individuals aged over 65 years have not been established.

Hepatic impairment

The metabolism of zolmitriptan is reduced in patients with hepatic impairment (see section 5.2). Therefore, for patients with moderate or severe hepatic impairment, a maximum dose of 5 mg in 24 hours is recommended.

Renal impairment

No dosage adjustment required (See section 5.2).

Paediatric population

Children (below 12 years of age)

The safety and efficacy of zolmitriptan tablets in children aged 0-12 years has not been evaluated. No data are available. Use of zolmitriptan in children is therefore not recommended.

Adolescents (12 - 17 years of age)

The efficacy of zolmitriptan tablets was not demonstrated in a placebo controlled clinical trial for patients aged 12 to 17 years. Use of zolmitriptan in adolescents is therefore not recommended.

Method of administration

To be taken by oral administration.

The tablet need not be taken with liquid; the tablet dissolves when placed on the tongue and is swallowed with the patient’s saliva. A drink of water is not required when taking Zolmitriptan Tablet. Zolmitriptan Tablet can be taken when water is not available thus allowing early administration of treatment for a migraine attack This

formulation may also be beneficial for patients who suffer from nausea and are unable to drink during a migraine attack, or for patients who do not like swallowing conventional tablets

4 CLINICAL PARTICULARS

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Uncontrolled hypertension.
- Ischaemic heart disease.
- Coronary vasospasm/Prinzmetal's angina.
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Concomitant administration of zolmitriptan with ergotamine, ergotamine, or derivatives or other 5-HT_1 receptor agonists.

4. CLINICAL PARTICULARS

4.4 Special warnings and precautions for use

Zolmitriptan should only be used where a clear diagnosis of migraine has been established. Care should be taken to exclude other potentially serious neurological conditions. There are no data on the use of zolmitriptan in hemiplegic or basilar migraine. 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 5-$HT_{1B/1D}$ agonists.

Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

In very rare cases, as with other 5-$HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. In patients with risk factors for ischaemic heart disease cardiovascular evaluation prior to commencement of treatment with this class of compounds, including zolmitriptan, is recommended (see section 4.3). 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.

As with other 5-$HT_{1B/1D}$ agonists, atypical sensations over the precordium (see section 4.8) have been reported after the administration of zolmitriptan. If chest pain or symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be taken until after appropriate medical evaluation has been carried out.

As with other 5-$HT_{1B/1D}$ 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 5-$HT_{1B/1D}$ agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

Patients with phenylketonuria should be informed that Zolmitriptan contains phenylalanine (a component of aspartame). Each 2.5 mg orally dispersible tablet contains 0.25 mg of aspartame. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.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 should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Serotonin Syndrome has been reported with combined use of triptans, and serotonergic drugs, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition, and diagnosis is likely when (in presence of a serotonergic agent) one of the following is observed:

- Spontaneous clonus,
- Inducible or ocular clonus with agitation or diaphoresis,
- Tremor and hyperreflexia,
- Hypertonia and body temperature >38°C and inducible or ocular clonus.

Careful observation of the patient is advised, if concomitant treatment with zolmitriptan and an SSRI or SNRI is clinically necessary, particularly during treatment initiation and dosage increases (see section 4.5).
Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

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

Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of zolmitriptan (for example beta-blockers, oral dihydroergotamine, and pizotifen).

The pharmacokinetics and tolerability of zolmitriptan, when administered as the conventional tablet, were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine. Concomitant administration of other 5-$HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment should be avoided.

Data from healthy subjects suggests there are no pharmacokinetic or clinically significant interactions between zolmitriptan and ergotamine. However, the increased risk of coronary vasospasm is a theoretical possibility. Therefore, it is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering any ergotamine containing product (see section 4.3).

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. Therefore, a maximum intake of 5mg zolmitriptan in 24 hours, is recommended in patients taking an MAO-A inhibitor.

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 (N-desmethylzolmitriptan) were doubled. A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking cimetidine. Based on the overall interaction profile, an interaction with inhibitors of the cytochrome P450 isoenzyme CYP 1A2 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).

Fluoxetine does not affect the pharmacokinetic parameters of zolmitriptan. Therapeutic doses of the specific serotonin reuptake inhibitors, fluoxetine, sertraline, paroxetine and citalopram do not inhibit CYP1A2. However, Serotonin Syndrome has been reported during combined use of triptans, and SSRIs (e.g.,fluoxetine, paroxetine, sertraline) and SNRIs (e.g., venlafaxine, duloxetine) (see section 4.4).

As with other 5-$HT_{1B/1D}$ agonists, there is the potential for dynamic interactions with the herbal remedy St John's wort (*Hypericum perforatum*) which may result in an increase in undesirable effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Zolmitriptan should be used in pregnancy only if the benefits to the mother justify potential risk to the foetus. There are no studies in pregnant women, but there is no evidence of teratogenicity in animal studies (see section 5.3).

Breast-feeding

Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be exercised when administering zolmitriptan to women who are breast-feeding.

4.7 Effects on ability to drive and use machines

There was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan. Zolmitriptan has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that somnolence may occur.

4 CLINICAL PARTICULARS

4.8 Undesirable effects

Summary of the safety profile

Zolmitriptan 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 4 hours of dosing and are no more frequent following repeated dosing.

Tabulated list of adverse reactions

Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following convesntion: Very common (≥1/10); Common (≥1/100 < 1/10); Uncommon (≥1/1,000 < 1/100); Rare (≥1/10,000 < 1/1,000); Very rare (<1/10,000 Not known (cannot be estimated from the available data).

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

System Organ Class	*Frequency*	*Undesirable Effect*
Immune system disorders	Rare	Anaphylaxis/Anaphylactoid Reactions; Hypersensitivity reactions
Nervous system disorders	Common	Abnormalities or disturbances of sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Myocardial infarction; Angina pectoris; Coronary vasospasm
Vascular disorders	Uncommon	Transient increases in systemic blood pressure
Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth Dysphagia
	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 and administration site conditions	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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

Management

The elimination half-life of zolmitriptan is 2.5 to 3 hours, (see section 5.2) and therefore monitoring of patients after overdose with zolmitriptan 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 the serum concentrations of zolmitriptan.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin (5-HT_1) agonists, ATC code: N02CC03

Mechanism of action

In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant 5-$HT_{1B/1D}$ receptors subtypes. Zolmitriptan is a high affinity 5-HT_{IB} and 5-HT_{ID} receptor agonist with modest affinity for 5-HT_{1A} receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_2-, 5-HT_3-, 5-HT_4-, $alpha_1$-, $alpha_2$-, or $beta_1$-, adrenergic; H_1-, H_2-, histaminic; muscarinic; $dopaminergic_1$, or $dopaminergic_2$ receptors. The 5-HT_{1D} receptor is predominately located presynaptically at both the peripheral and central synapses of the trigeminal nerve and preclinical studies have shown that zolmitriptan is able to act at both these sites.

Clinical efficacy and safety

One controlled clinical trial in 696 adolescents with migraine failed to demonstrate superiority of zolmitriptan tablets at doses of 2.5 mg, 5 mg and 10 mg over placebo. Efficacy was not demonstrated.

5. PHARMACOLOGICAL PROPERTIES

5.2 Pharmacokinetic properties

Absorption

Following oral administration of zolmitriptan conventional tablets, zolmitriptan is rapidly and well absorbed (at least 64%) in man. The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (N-desmethylzolmitriptan) which is also a 5-$HT_{1B/1D}$ agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan.

In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite, the N-desmethylzolmitriptan, display dose-proportional AUC and C_{max} over the dose range 2.5 to 50 mg. Absorption of zolmitriptan is rapid with 75% of C_{max} achieved within 1 hour, and plasma concentrations are sustained subsequently for 4 to 6 hours. Zolmitriptan absorption is unaffected by the presence of food. There was no evidence of accumulation on multiple dosing of zolmitriptan.

Biotransformation and elimination

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 is pharmacologically active whilst the others are not. Zolmitriptan is metabolised by CYP1A2, forming N-desmethylzolmitriptan. The active metabolite is then further metabolised through MAO-A enzyme system. Plasma concentrations of the N-desmethylated metabolite 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 indole acetic 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 active metabolite (N-desmethylzolmitriptan), 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 ($t_{½}$) 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 $t_{½}$ values for the N-desmethylzolmitriptan 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 intravenous 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.

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 with zolmitriptan alone (see section 4.5).
Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.
Selegiline, an MAO-B inhibitor, and fluoxetine (a selective serotonin reuptake inhibitor; SSRI) had no effect on the pharmacokinetic parameters of zolmitriptan (see section 4.4).

Zolmitriptan was demonstrated to be bioequivalent with the conventional tablet in terms of AUC and C_{max} for zolmitriptan and its active metabolite desmethylzolmitriptan. Clinical pharmacology data show that the t_{max} for zolmitriptan can be later for the orally dispersible tablet (range 0.6 to 5h, median 3h) compared to the conventional tablet (range 0.5 to 3h, median 1.5h). The t_{max} for the active metabolite was similar for both formulations (median 3h).

<u>Renal impairment</u>
Renal clearance of zolmitriptan and all 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.

<u>Elderly</u>
The pharmacokinetics of zolmitriptan in healthy elderly subjects were similar to those in healthy young volunteers.

5 PHARMACOLOGICAL PROPERTIES

5.3 Preclinical safety data

An oral teratology study of a zolmitriptan tablets has been conducted. At the maximum tolerated doses of a zolmitriptan tablets, 1200 mg/kg/day (AUC 605 μg/ml.h: approx. 3700 x AUC of the human maximum recommended daily intake of 15 mg) and 30 mg/kg/day (AUC 4.9 μg/ml.h: approx. 30 x AUC of the human maximum recommended daily intake of 15 mg) in rats and rabbits, respectively, no signs of teratogenicity were apparent.

Five genotoxicity tests have been performed. It was concluded that a zolmitriptan tablets 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 tumorogenicity.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Magnesium Aluminometasilicate

Hydroxy Propyl Cellulose

Aspartame (E951)

Sodium Lauril Sulfate

Basic Butylated Methacrylate Copolymer

Talc

Colloidal anhydrous silica

Magnesium stearate

Peppermint Flavour (containing maltodextrin, natural flavours and modified corn starch)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Peelable cold-formed aluminium blisters.

Pack sizes:

6 orodispersible tablets

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6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0563

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2025

10 DATE OF REVISION OF THE TEXT

21/02/2025