SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg zolmitriptan
Excipient with known effect:
102.50 mg lactose per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Yellow coloured, round, biconvex film-coated tablets debossed with 497 on one side and deep break line on other side (diameter approximately: 7 mm).
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zolmitriptan is indicated for the acute treatment of migraine headache with or without aura. It is not indicated for prophylaxis of migraine.

4.2 Posology and method of administration

Posology

The recommended dose of zolmitriptan to treat a migraine attack is 2.5 mg. It is advisable that Zolmitriptan is taken as early as possible after the onset of migraine headache but it is also effective if taken at a later stage.

If symptoms of migraine should recur within 24 hours following an initial response, a second dose may be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose. If a patient does not respond to the first dose, it is unlikely that a second dose will be of benefit in the same attack.

If a patient does not achieve satisfactory relief with 2.5 mg doses, for subsequent attacks 5 mg doses of zolmitriptan could be considered. 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.

Special populations

Patients with hepatic impairment
Metabolism is reduced in patients with hepatic impairment (see section 5.2). Patients with mild hepatic impairment require no dose adjustment. However, for patients with moderate or severe hepatic impairment, a maximum dose of 5 mg in 24 hours is recommended.

Patients with renal impairment
No dosage adjustment required in patients with a creatinine clearance of more than 15 ml/min. (Section 5.2).

Interactions requiring dose adjustment (see section 4.5).
For patients taking MAO-A inhibitors, a maximum dose of 5 mg in 24 hours is recommended.

A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking cimetidine.

A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking specific inhibitors of CYP 1A2 such as fluvoxamine and the quinolones (e.g. ciprofloxacin).

Paediatric population

Children (under 12 years of age)
Safety and efficacy of zolmitriptan tablets in paediatric patients have not been evaluated. 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.

Older people
The safety and efficacy of zolmitriptan in individuals aged over 65 years have not been evaluated. Use of Zolmitriptan in the elderly is therefore not recommended.

Method of administration
For oral use.
Zolmitriptan tablets should be swallowed with a drink of water.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• Moderate to severe hypertension, and mild uncontrolled hypertension.

• Ischaemic heart disease. Coronary vasospasm/ Prinzmetal's angina.

• A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

• Concomitant administration of zomitriptan with ergotamine or ergotamine derivatives (including methysergide), sumatriptan, naratriptan or other 5-HT_1 receptor agonists.

4.4 Special warnings and precautions for use

Zolmitriptan should only be used where a clear diagnosis of migraine has been established. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. Zolmitriptan is not indicated for use in hemiplegic, basilar or ophtalmoplegic migraine. Migraneurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with $5HT_{1B/1D}$ 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 $5HT_{1B/1D}$ agonists, coronary vasopasm, angina pectoris and myocardial infarction have been reported. In patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus, heredity), cardiovascular evaluation prior to commencement of treatment with this class of compounds, including "Zolmitriptan" is recommended (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.

As with other $5HT_{1B/1D}$ agonists, atypical sensations, such as heaviness, pressure or tightness 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 $5HT_{1B/1D}$ 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 $5HT_{1B/1D}$ agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

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 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). Careful observation of the patient is advised, if concomitant treatment with zolmitriptan and an SSRI or SNRI is clinically warranted, particularly during treatment initiation and dosage increases (see section 4.5).

This medicinal product contains lactose. Patients with rare hereditary problems of galacotose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine. Concomitant administration of other $5HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours with the use of other $5\text{-}HT_{1B/1D}$ agonists should also be avoided.

Data from healthy subjects suggest there are no pharmacokinetic or clinically significant interactions between zolmitriptan and ergotamine, however, the increased risk of coronary vasospasm is a theoretical possibility, and concomitant administration is contraindicated. 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 preparation (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 5 mg zolmitriptan in 24 hours is recommended in patients taking an MAO-A inhibitor. The medicinal products should not be used together if doses of moclobemide higher than 150 mg twice a day are administered.

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 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 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).

Selegiline (a MAO-B inhibitor) and 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).

Zolmitriptan could delay the absorption of other medicinal products.

As with other $5HT_{IB/ID}$ 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

The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct teratogenic effects. However, some findings in embryo-toxicity studies suggested impaired embryo viability. Administration of zolmitriptan during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus (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. Infant exposure should be minimised by avoiding breast feeding for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

In a small group of healthy individuals there was no significant impairment of performance of psychomotor tests with doses up to 20 mg of zolmitriptan. Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack.

4.8 Undesirable effects

Adverse reactions are typically transient 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.

The following table lists the adverse reactions associated with zolmitriptan therapy.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:
Very common (≥1/10); Common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System organ class	**Frequency**			
	Common	**Uncommon**	**Rare**	**Very rare**
Immune System Disorders			Anaphylaxis/ Analphylactoid reactions Hypersensitivity reactions	
Nervous System Disorders	Abnormalities or disturbances of sensation Dizziness Headache Hyperaesthesia Paraesthesia Somnolence Warm sensation			
Cardiac Disorders	Palpitations	Tachycardia		Angina pectoris Coronary Vasospasm Myocardial Infarction
Vascular Disorders		Transient increases in systemic blood pressure		
Gastrointestinal Disorders	Abdominal Pain Dry mouth Nausea			Bloody diarrhoea Gastrointestinal infarction or

	Vomiting Dysphagia			necrosis Gastrointestinal ischaemic events Ischaemic colitis Splenic Infarction
Skin and subcutaneous tissue disorders			Angiodema Urticaria	
Musculoskeletal and Connective Tissue Disorders	Muscle weakness Myalgia			
Renal and Urinary Disorders		Polyuria Increased urinary frequency		Urinary Urgency
General Disorders and Administration Site Conditions	Asthenia Heaviness, tightness, pain or pressure in throat, neck limbs or chest			

Certain symptoms may be part of the migraine attack itself.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see section 5.2) and therefore monitoring of patients after overdose with Zolmitriptan tablets 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: Analgesics; Antimigraine preparations;
Selective serotonin ($5HT_1$) agonists
ATC code: N02CC03

In preclinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant 5-$HT_{IB/1D}$ receptor subtypes. Zolmitriptan is a high affinity human recombinant 5-HT_{IB} receptor agonist, with modest affinity for 5-HT_{IA} receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at other 5-HT receptor subtypes (5-HT_2, 5-HT_3, 5-HT_4) or adrenergic, histaminic, muscarinic or dopaminergic receptors. The $5HT_{1D}$ 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 of these sites.

In animal models, the administration of zolmitriptan causes vasoconstriction in the carotid arterial circulation. In addition, experimental studies in animals suggest that zolmitriptan inhibits central and peripheral trigeminal nerve activity with inhibition of neuropeptide release (calcitonin gene related peptide (CGRP), vasoactive intestinal peptide (VIP) and Substance P).

In clinical studies with zolmtriptan conventional tablets the onset of efficacy is apparent from one hour, with increasing efficacy being noted between 2 and 4 hours on headache and other symptoms of migraine such as nausea, photophobia and phonophobia.

Zolmitriptan, when administered as conventional oral tablets, is consistently effective in migraine with or without aura and in menstrually associated migraine. Zolmitriptan, when administered as conventional oral tablets, if taken during the aura, has not been demonstrated to prevent the migraine headache and therefore Zolmitriptan should be taken during the headache phase of migraine.

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.

5.2 Pharmacokinetic properties

Following oral administration of Zolmitriptan conventional tablets, zolmitriptan is rapidly and well absorbed (at least 64%) after oral administration to man. The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (the N-desmethyl metabolite) which is also a $5HT_{1B/1D}$ receptor 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-desmethyl metabolite, display dose-proportional AUC and C_{max} over the dose range 2.5 to 50 mg. Absorption of zolmitriptan is rapid. In healthy volunteers, 75% of C_{max} is achieved within 1 hour, and after this the concentration of zolmitriptan in plasma is maintained at approximately this level until 4-6 hours after dosing.

Zolmitriptan absorption is unaffected by the presence of food. There was no evidence of accumulation on multiple dosing of zolmitriptan.

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 active whilst the others are not. 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.

Plasma concentration of zolmitriptan and its metabolites are lower in the first 4 hours after medicinal product administration during a migraine compared with a migraine-free period, suggesting delayed absorption consistent with the reduced rate of gastric emptying observed during a migraine attack.

A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and Cmax 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 Cmax 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 (t½) 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 t½ values for the 183C91 metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively.

The metabolism of zolmitriptan is reduced in hepatic impairment in proportion to the extent of the impairment.

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 of zolmitriptan and the N-desmethyl metabolite 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 all its metabolites is reduced (7-8 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 with zolmitriptan alone (see section 4.5 for precautions regarding ergotamine use).

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 for warnings and precautions regarding concomitant use with SSRIs).

The pharmacokinetics of zolmitriptan in healthy elderly subjects were similar to those in healthy young volunteers.

5.3 Preclinical safety data

Effects in non-clinical studies for single and repeat dose toxicity were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

An oral teratology study of zolmitriptan has been conducted. At the maximum tolerated doses of zolmitriptan, 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 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 tumorogenicity.

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

As with other $5HT_{1B/1D}$ receptor agonists, zolmitriptan is also bound to melanin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose
Cellulose microcrystalline
Sodium Starch Glycolate (type A)
Magnesium Stearate

Tablet Coat
Hypromellose
Titanium dioxide (E 171)
Macrogol 400
Macrogol 8000
Iron Oxide Yellow (E 172)

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

Cold form aluminium foil blisters with plain aluminium foil lidding in cartons containing 2 film-coated tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited,
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Kenton, HA3 OBU.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0282

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2025

10 DATE OF REVISION OF THE TEXT

21/02/2025