SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mg
Each film-coated tablet contains 5.0 mg zolmitriptan
Excipient: Lactose, anhydrous 205.00 mg per tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
5 mg
Pink coloured, round, biconvex film-coated tablets debossed with 498 on one side and plain on other side (diameter approximately: 8.5 mm).

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.

If symptoms persist or return within 24 hours, a second dose 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 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, subsequent attacks can be treated with 5 mg doses of zolmitriptan. In those patients who respond, significant efficacy is apparent within 1 hour of dosing. Caution is advised due to an increased incidence of undesirable effects. A controlled clinical study failed to demonstrate superiority of the 5 mg dose over the 2.5 mg dose. Nevertheless a 5 mg dose may be of benefit for some patients.

Zolmitriptan is equally effective whenever the tablets are taken during a migraine attack; although it is advisable that zolmitripan tablets are taken as early as possible after the onset of a 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. Not more than 2 doses of Zolmitriptan Film-coated Tablets should be taken in any 24 hour period.

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. (see Section 5.2)
Interactions requiring dose adjustment (see section 4.5)
For patients taking MAO-A inhibitors, specific inhibitors of CYP1A2 such as fluvoxamine and the quinolones (eg ciprofloxacin), or for patients taking cimetidine, a maximum dose of 5 mg zolmitriptan in 24 hours is recommended.
Paediatric population
Children (under 12 years of age)
The efficacy of Zolmitriptan tablets in children aged less than 12 years have not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

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. Therefore the use of zolmitriptan tablets in this age group is 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:
To be taken by oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance zolmitriptan 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 zomitriptanwith ergotamine or ergotamine derivatives 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. There is no data on the use of Zolmitriptan in hemiplegic or basilar 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 Contraindications). 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 Undesirable Effects) 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.

Excessive use of an acute anti-migraine medicinal product may lead to an increased frequency of headache, potentially requiring withdrawal of treatment. 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), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and

opioid products (e.g. Buprenorphine). 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, 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, the Lapp 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 b.i.d. 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 (eg, 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 Breast-feeding

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 justifies potential 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.

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 of zolmitriptan. Use in patients is unlikely to result in the impairment of their ability to drive or operate machinery. However it should be taken into account that somnolence may occur.

4.8 Undesirable effects

Zolmitriptan Tablets 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.

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 Vomiting Dysphagia			Bloody diarrhoea Gastrointestinal infarction or necrosis Gastrointestinal ischaemic events Ischaemic colitis Splenic Infarction
Skin and subcutaneous			Angiodema Urticaria	

tissue disorders				
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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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: Selective serotonin (5HT1) agonists. ATC code: N02CC03

In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant $5HT_{1B}$ and $5HT_{1D}$ receptor subtypes. Zolmitriptan is a high affinity $5HT_{1B/1D}$ receptor agonist with modest affinity for $5HT_{1A}$ receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at $5HT_2$-, $5HT_3$-, $5HT_4$-, $alpha_1$-, $alpha_2$-, or $beta_1$-, adrenergic; H_1-, H_2-, histaminic; muscarinic; $dopaminergic_1$, or $dopaminergic_2$ 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 these sites.

In clinical studies 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 is consistently effective in migraine with or without aura and in menstrually associated migraine. Zolmitriptan, if taken during the aura, has not been demonstrated to prevent migraine headache and therefore Zolmitriptan Film-coated Tablets 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

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 (183C91, the N-desmethyl metabolite) which is also a $5HT_{1B/1D}$ 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 183C91, display dose-proportional AUC and C_{max} over the dose range 2.5 to 50 mg. Absorption 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 is 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 (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 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 drug administration during a migraine compared with a migraine-free period, suggesting

delayed absorption consistent with a 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.

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.

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.

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

In preclinical acute and chronic toxicity studies, toxic effects were only observed at dosages considerably above the maximum therapeutic dose in humans.
Results from in vitro and in vivo genotoxicity studies show that, under the conditions of clinical use, no genotoxic effects of zolmitriptan are anticipated.

In long-term studies to investigate the tumorigenic potential in mice and rats, no tumours relevant to clinical use were found.
As with other $5HT_{1B/1D}$ receptor agonists, zolmitriptan is also bound to melanin.
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

5 mg
Tablet core
Lactose anhydrous
Cellulose microcrystalline
Sodium Starch Glycolate type A
Magnesium Stearate

Tablet Coat
Hypromellose
Titanium dioxide (E 171)
Macrogol 400
Macrogol 8000
Iron Oxide Red (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 3, 6 or 12 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0083

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