SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zomig Rapimelt Migraine Control 2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 2.5 mg of zolmitriptan.

Excipient with known effect
Each orodispersible table contains 5 mg of aspartame (E951).
Each orodispersible tablet contains 0.0000032 mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oro-dispersible tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zomig Rapimelt Migraine Control is indicated for the acute treatment of migraine with or without aura.

Zomig Rapimelt Migraine Control should only be used where there is a clear diagnosis of migraine.

4.2 Posology and method of administration

Posology

Adults (18-65 years of age)

The recommended dose of Zomig Rapimelt Migraine Control to treat a migraine attack is 2.5 mg.

If symptoms persist or return 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.

Zolmitriptan is equally effective whenever the tablets are taken during a migraine attack; although it is advisable that Zomig Rapimelt Migraine Control 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 Zomig Rapimelt Migraine Control in a 24 hour period should not exceed 5 mg.
If no relief is obtained after taking 5 mg then the patient should be referred to a doctor.
Zomig Rapimelt Migraine Control is not indicated for prophylaxis of migraine.

*Paediatric population (*Children below the age of 12 years)
The safety and efficacy of Zomig Rapimelt Migraine Control in children aged 0-12 years has not yet been established. No data are available. Use of Zomig Rapimelt Migraine Control in children is therefore not recommended.

Adolescents (12 - 17 years of age)
The efficacy of Zomig Rapimelt Migraine Control tablets was not demonstrated in a placebo controlled clinical trial for patients aged 12 to 17 years. Use of Zomig Rapimelt Migraine Control in adolescents is therefore not recommended.

Elderly
The safety and efficacy of Zomig Rapimelt Migraine Control in individuals aged over 65 years have not been established. Zomig Rapimelt Migraine Control tablets should not be used in patients aged over 65 years of age.

Hepatic impairment
Metabolism is reduced in patients with hepatic impairment (see section 5.2. The use of Zomig Rapimelt Migraine Control is contraindicated in patients with severe hepatic impairment (see section 4.3 and section 5.2). No dosage adjustment is required for patients with moderate hepatic impairment.

Renal impairment
No dosage adjustment required (see section 5.2). The use of Zomig Rapimelt Migraine Control is contraindicated in patients with severe renal impairment (see section 4.3 and section 5.2).
Method of administration
Zomig Rapimelt Migraine Control is for oral use only.

Zomig Rapimelt Migraine Control rapidly dissolves when placed on the tongue and is swallowed with the patient's saliva. A drink of water is not required when taking Zomig Rapimelt Migraine Control. Zomig Rapimelt Migraine Control 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.

4.3 Contraindications

Zomig Rapimelt Migraine Control is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known hypertension.
- Ischaemic heart disease (including previous myocardial infarction or angina).
- Severe hepatic or severe renal impairment.
- Epilepsy or a history of seizures.
- Atypical migraine (including hemiplegic or basilar migraine).
- Peripheral vascular disease.
- Coronary vasospasm/Prinzmetal's angina.
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Cardiac arrhythmias (including Wolff-Parkinson-White syndrome).
- Concomitant administration of Zomig Rapimelt Migraine Control tablets with ergotamine or ergotamine derivatives or other 5-HT_1 receptor agonists.

4.4 Special warnings and precautions for use

Zomig Rapimelt Migraine Control should only be used where a clear diagnosis of migraine has been established. Pharmacy supply of Zomig Rapimelt Migraine Control is therefore not appropriate if the patients' first migraine attack occurred within the last 12 months; pharmacy supply is restricted to patients with an established pattern of at least five migraine attacks.

Patients having 4 or more migraines a month should be referred to a doctor.

Care should be taken to exclude other potentially serious neurological conditions.

Patients should be referred to a doctor for further assessment if any of the following apply: their migraine symptoms do not disappear between attacks (migraine is episodic); they are over the age of 50 and experiencing migraine for the first time; their migraine headache lasts for longer than 24 hours; they have a change in their usual migraine symptoms, or their migraines increase in frequency.

There are no data on the use of Zomig Rapimelt Migraine Control in hemiplegic or basilar migraine (see section 4.3). 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.

Zomig Rapimelt Migraine Control should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways (see section 4.3).

In very rare cases, as with other $5HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. Patients should be assessed for risk of undiagnosed cardiovascular disease prior to receiving Zomig Rapimelt Migraine Control. The following risk factors for cardiovascular disease should be taken into account:

- Diabetes mellitus
- Regular smoker (10 or more daily)
- Family history of Ischaemic Heart Disease
- Hypercholesterolaemia
- Post-menopausal female
- Male aged over 40 years
- Body Mass Index > 30 kg/m^2

Patients with three or more of the above risk factors should not receive Zomig Rapimelt Migraine Control until they have been further assessed by a doctor. 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.

A new diagnosis of migraine or change in severity of symptoms may imply contraindication to the combined oral contraceptive pill, especially in the presence of one or more cardiovascular risk factors or migraine with aura. Women taking a combined oral contraceptive should consult a doctor if the onset of migraine is recent or if their symptoms become more severe.

As with other $5HT_{1B/1D}$ agonists, atypical sensations such as heaviness, tightness, pain or pressure 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 Zomig Rapimelt Migraine Control tablets.

Patients with phenylketonuria should be informed that Zomig Rapimelt Migraine Control contains phenylalanine (a component of aspartame). Each 2.5 mg orally dispersible tablet contains 2.81 mg of phenylalanine. 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 Zomig and an SSRI or SNRI is clinically warranted, 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.

Patients taking St John's wort should not take Zomig Rapimelt Migraine Control without first consulting a doctor (see section 4.5).

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

This medicine contains 0.0000032 mg of benzyl alcohol in each orodispersible tablet. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

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, pizotifen).

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

Data from healthy subjects suggest there are no pharmacokinetic or clinically significant interactions between Zomig 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 Zomig. Conversely it is advised to wait at least six hours following use of Zomig 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 'Zomig Rapimelt Migraine Control' in 24 hours is recommended in patients taking an MAO-A inhibitor.

Following the administration of cimetidine, a general P450 inhibitor, the halflife of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition the halflife and AUC of the active N-desmethylated metabolite (N-desmethylzolmitriptan) were doubled. A maximum dose of 5 mg 'Zomig Rapimelt Migraine Control' 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).

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 $5HT_{1b/1d}$ 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

Zomig Rapimelt Migraine Control should only be used in pregnancy on the advice of a doctor, and 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,

Zomig Rapimelt Migraine Control is not to be used in breast-feeding women except on the advice of a doctor.

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. Zomig Rapimelt Mirgraine Control has no or negligible influence on the ability to drive and use machines. However it should be taken into account that somnolence may occur.

4.8 Undesirable effects

Summary of the safety profile
Zomig 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 convention: 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); Not known (cannot be estimated from the available data). The following undesirable effects have been reported following administration with zolmitriptan:

System Organ Class	**Frequency**	**Undesirable Effect**
Immune system disorders	Rare	Anaphylaxis/Anaphylactoid Reactions; Hypersensitivity reactions.
Nervous system disorder	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.
Gastrointestinal disorders	Common	Abdominal pain; Dry mouth; Nausea; Vomiting; 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 Zomig Rapimelt Migraine

Control 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 ($5HT_1$) 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 $5HT_{1B}$ 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.
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.

5.2 Pharmacokinetic properties

Following oral administration of Zomig 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 $5HT_{IB/1D}$ 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 N-desmethylzolmitriptan, 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 (N-desmethylzolmitriptan) 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 N-desmethylzolmitriptan are approximately half those of the parent drug, hence it would therefore be expected to contribute to the therapeutic action of Zomig Rapimelt Migraine Control. 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 N-desmethylzolmitriptan 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 (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 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.

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.

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.

Zomig Rapimelt Migraine Control was demonstrated to be bioequivalent with the conventional tablet in terms of AUC and C_{max} for zolmitriptan and its active

metabolite N-desmethyl zolmitriptan. 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).

Elderly

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

5.3 Preclinical safety data

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

Five genotoxicity tests have been performed. It was concluded that Zomig Rapimelt Migraine Control 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

The following excipients are contained in each Zomig Rapimelt Migraine Control orodispersible tablet as indicated:

Aspartame (E951)
Citric Acid Anhydrous
Silica Colloidal Anhydrous
Crospovidone
Magnesium stearate
Mannitol (E421)
Microcrystalline Cellulose
Orange Flavour (contains benzyl alcohol)
Sodium Hydrogen Carbonate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

PVC aluminium/aluminium blister pack of 2 tablets

6.6 Special precautions for disposal

The blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil). The Zomig Rapimelt Migraine Control tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva.
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Grünenthal Limited
TOR Building,
Saint Cloud Way,
Maidenhead,
Berkshire, SL6 8BN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 21727/0087

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/01/2025

10 DATE OF REVISION OF THE TEXT

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