

1. NAME OF THE MEDICINAL PRODUCT

Zomig Rapimelt 2.5 mg orodispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablets contains 2.5 mg of zolmitriptan.

Excipients with known effect

Each orodispersible tablet 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

Orodispersible tablets.

Round, white uncoated orodispersible tablets impressed with 'Z' on one side with a bevelled edge.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended dose of Zomig Rapimelt to treat a migraine attack is 2.5 mg. It is advisable that Zomig Rapimelt orally dispersible tablets are taken as early as possible after the onset of migraine headache but they are 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 Zomig Rapimelt could be considered.

The total daily intake should not exceed 10 mg. Not more than 4 doses of Zomig 2.5 mg Rapimelt should be taken in any 24 hour period.

Zomig Rapimelt is not indicated for prophylaxis of migraine.

Paediatric population

Use in Children (under 12 years of age)

The safety and efficacy of Zomig Rapimelt in children aged 0-12 years has not yet been established. No data are available. Use of Zomig Rapimelt in children is therefore not recommended.

Use in Adolescents (12 - 17 years of age inclusive)

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

Elderly

The safety and efficacy of Zomig Rapimelt in individuals aged over 65 years have not been established. Use of Zomig Rapimelt in the elderly is therefore not recommended.

Hepatic impairment

Patients with mild or moderate hepatic impairment require no dose adjustment, however for patients with severe hepatic impairment, a maximum dose of 5 mg in 24 hours is recommended.

Renal impairment

No dosage adjustment required in patients with a creatinine clearance of more than 15 ml/min (see section 4.3 and section 5.2).

Method of administration

To be taken orally.

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

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

Moderate or severe hypertension, and mild uncontrolled hypertension.

This class of compounds (5HT_{1B/1D} receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore Zomig Rapimelt should not be given to patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or signs consistent with ischaemic heart disease.

Concurrent administration of ergotamine, derivatives of ergotamine (including methysergide), sumatriptan, naratriptan and other 5HT_{1B/1D} receptor agonists with zolmitriptan is contraindicated (see section 4.5).

Zomig Rapimelt should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Zomig Rapimelt is contraindicated in patients with a creatinine clearance of less than 15 ml/min.

4.4 Special warnings and precautions for use

Zomig Rapimelt 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. Zomig Rapimelt is not indicated for use in hemiplegic, basilar or ophthalmoplegic 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.

Zomig Rapimelt 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 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 compound, including Zomig Rapimelt, is recommended (see section 4.3). Such patients include postmenopausal women, males over 40 and patients with risk factors for coronary artery disease.

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} receptor agonists, heaviness, pressure or tightness over the precordium (see section 4.8) have been reported after the administration of zolmitriptan. If symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be given and appropriate evaluation should be 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.

The dose recommendation for zolmitriptan should not be exceeded.

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

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 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.

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 daily headaches despite (or because of) the regular use of headache medications.

The safety and efficacy of Zomig Rapimelt in individuals aged over 65 years have not been established. Use of Zomig Rapimelt in the elderly is therefore not recommended.

Refer to sections 4.2 and 5.2 when treating patients with hepatic impairment.

Zomig Rapimelt contains 5 mg aspartame in each 2.5 mg orodispersible tablet. Aspartame is a source of phenylalanine. Patients with phenylketonuria should be informed that Zomig Rapimelt orally dispersible tablets contain 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.

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

Zomig Rapimelt 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

Interaction studies were performed with caffeine, ergotamine, dihydroergotamine, paracetamol, metoclopramide, pizotifen, fluoxetine, rifampicin and propranolol and no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

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, and concomitant administration is contraindicated. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering Zomig Rapimelt. Conversely it is advised to wait at least six hours following use of Zomig Rapimelt before administering an ergotamine containing product (see section 4.3).

Concomitant administration of other 5HT_{1B/1D} agonists within 24 hours of Zomig treatment should be avoided.

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 in 24 hours, is recommended in patients taking a MAO-A inhibitor. The drugs should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

Following administration of cimetidine, a general P₄₅₀ inhibitor, the half life and AUC of zolmitriptan and its active metabolite were approximately doubled. A maximum dose of 5 mg Zomig Rapimelt in 24 hours is recommended in patients

taking cimetidine. Based on the overall interaction profile, an interaction with specific inhibitors of CYP 1A2 cannot be excluded. Therefore, the same dosage reduction is recommended with compounds of this type, such as fluvoxamine and the quinolones (e.g. ciprofloxacin). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Selegiline (a MAO-B inhibitor) and fluoxetine (an SSRI) did not result in any pharmacokinetic interaction with zolmitriptan. However, Serotonin Syndrome has been reported with 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} receptor agonists, zolmitriptan could delay the absorption of other drugs.

Undesirable effects may be more common during concomitant use of Zomig and herbal preparations containing St John's wort.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medical product for use in human pregnancy has not been established. Evaluation of experimental animals studies does not indicate direct teratogenic effects. However, some findings in embryotoxicity studies suggested impaired embryo viability. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

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 Zomig Rapimelt 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 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

Summary of the safety profile

Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment. Possible adverse reactions tend to occur within four 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 ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$).

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

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:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms

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

Management

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 Zomig Rapimelt orally dispersible 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

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 5HT₂-, 5HT₃-, 5HT₄-, α ₁-, α ₂-, or β ₁-, adrenergic; H₁-, H₂-, histaminic; muscarinic; dopaminergic₁, or dopaminergic₂, receptors.

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 Zomig 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 Zomig Rapimelt should be taken during the headache phase of migraine.

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%) 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 is rapid with 75% of C_{max} achieved within 1 hour in healthy volunteers 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.

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 the reduced rate of gastric emptying observed during a migraine attack.

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. Metabolism of zolmitriptan is dependent on CYP1A2 and the metabolism of the active metabolite N-desmethylzolmitriptan is via the monoamine oxidase A (MAOA) enzyme system. 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 Zomig. 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 (T_{1/2}) of Zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding T_{1/2} values for the 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 quarter 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.

The metabolism of zolmitriptan is reduced in hepatic impairment in proportion to the extent of the impairment. Zolmitriptan AUC and C_{max} were increased by 226% and 50%, respectively and the half life was prolonged to 12 hours in subjects with severe liver disease compared to healthy subjects. Exposure to the metabolites, including the active metabolite was reduced.

Selegiline, a MAO-B inhibitor, and fluoxetine had no effect on the pharmacokinetic parameters of zolmitriptan (see section 4.4).

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

The Zomig Rapimelt orally dispersible formulation was found to be bioequivalent with the conventional tablet in terms of AUC and $C_{\max}$ for zolmitriptan and its active metabolite (N-desmethylzolmitriptan). The time to maximum plasma concentration following administration of Zomig Rapimelt is similar for the active metabolite (N-desmethylzolmitriptan) but can be prolonged for zolmitriptan with this formulation relative to the conventional tablet. In a clinical pharmacology study to compare the two formulations, for the active metabolite N-desmethylzolmitriptan, the $t_{\max}$ ranged from 0.75 to 5 hours (median 3.0 hours) for conventional tablet, and 1.0 to 6 hours (median 3.0 hours) for the orally dispersible tablet, whereas for zolmitriptan the ranges were 0.5 to 3 hours (median 1.5 hours) and 0.6 to 5 hours (median 3.0 hours) respectively. However, plasma concentrations of zolmitriptan for the orally dispersible and conventional tablet formulations are similar up to 45 minutes post dose, the period of most importance for initial absorption following administration.

5.3 Preclinical safety data

Preclinical effects in single and repeat dose toxicity studies were observed only at exposures well in excess of the maximum human exposure.

The findings from in vitro and in vivo genetic toxicity studies show that genotoxic effects of zolmitriptan are not to be expected under the conditions of clinical use.

No tumours relevant to the clinical use were found in mouse and rat carcinogenicity studies.

As with other 5HT_{1D/1B} receptor agonists, zolmitriptan binds to melanin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Anhydrous Citric acid
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°C

6.5 Nature and contents of container

Tablets in peelable aluminium laminate blister packs containing: 2, 6 (with or without wallet) or 12 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil).

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 Pharma Limited.
4045 Kingswood Road
Citywest Business Park
Citywest
Co Dublin
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PA 2242/004/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 1999

Date of latest renewal: 30th November 2006

10. DATE OF REVISION OF THE TEXT

August 2024