Zomig Rapimelt

1. NAME OF THE MEDICINAL PRODUCT

Zomig Rapimelt 2.5mg orodispersible tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zomig Rapimelt is presented as orodispersible tablets containing 2.5mg of zolmitriptan.

3. PHARMACEUTICAL FORM

Zomig Rapimelt: Orodispersible tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

The Zomig Rapimelt orodispersible 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 orodispersible tablet. Zomig Rapimelt orodispersible 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.

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 achieve satisfactory relief with 2.5 mg doses, subsequent attacks can be treated with 5 mg doses of Zomig Rapimelt.

Significant efficacy is apparent within 1 hour of dosing.

Zomig Rapimelt is equally effective whenever taken during a migraine attack; although it is advisable that Zomig Rapimelt tablets are 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, in a 24 hour period, should not exceed 10 mg.

Zomig Rapimelt is not indicated for prophylaxis of migraine.

Use in Patient Subgroups

Zomig Rapimelt is consistently effective in migraine, with or without aura, and in menstrually associated migraine. The efficacy of Zomig Rapimelt is also unaffected by gender, duration of the attack, pre-treatment nausea and concomitant use of common prophylactic migraine drugs.

Use in Children (under 12 years of age)

Safety and efficacy of zolmitriptan tablets in paediatric patients have not been evaluated. Use of Zomig Rapimelt in children is therefore not recommended.

Adolescents (12 - 17 years of age)

The efficacy of Zomig tablets was not demonstrated in a placebo controlled clinical trial for patients aged 12 to 17 years. The profile and frequency of adverse events are consistent with Zomig Rapimelt Tablet use in adults. Use of Zomig Rapimelt tablets in adolescents is therefore not recommended.

Use in Patients Aged Over 65 years

Safety and efficacy of 'Zomig Rapimelt' in individuals aged over 65 years have not been systematically evaluated.

Patients with Hepatic Impairment

Metabolism is reduced in patients with hepatic impairment (See Pharmacokinetic Properties section). Therefore 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 (see Pharmacokinetic Properties section).

4.3 Contraindications

Zomig Rapimelt is contraindicated in patients with:

- Known hypersensitivity to any component of the product.
- Uncontrolled hypertension.
- Ischaemic heart disease.
- Coronary vasospasm/Prinzmetal's angina.
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Concomitant administration of Zomig Rapimelt with ergotamine or ergotamine derivatives or other 5-HT₁ receptor agonists.

4.4 Special warnings and special precautions for use

Zomig Rapimelt should only be used where a clear diagnosis of migraine has been established. Care should be taken to exclude other potentially serious neurological conditions. There are no data on the use of Zomig Rapimelt 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.

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, this class of compounds ($5HT_{1B/1D}$ agonists), has been associated with coronary vasospasm, angina pectoris and myocardial infarction. In patients with risk factors for ischaemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including Zomig Rapimelt, is recommended (see Contraindications section). 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 over the precordium (see Possible Adverse Reactions section) 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.

Patients with phenylketonuria should be informed that Zomig Rapimelt orodispersible tablets contain phenylalanine (a component of aspartame). Each 2.5mg orodispersible tablet contains 2.81 mg of phenylalanine.

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 $>38^{\circ}$ 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 Interactions section).

Withdrawal of the serotonergic drugs is a key therapeutic principle. Further treatment depends on the type and severity of the symptoms.

Excessive use of an acute anti-migraine medicinal product may lead to an increased frequency of headache, potentially requiring withdrawal of treatment.

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 (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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 Zomig Rapimelt (for example beta blockers, oral dihydroergotamine, pizotifen).

The pharmacokinetics and tolerability of Zomig Rapimelt 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 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 Contraindications).

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5mg Zomig Rapimelt in 24 hours is recommended in patients taking a MAO-A inhibitor.

Following the administration of cimetidine, a general P450 inhibitor, the half life of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition, the half life and AUC of the active, N-desmethylated, metabolite (N-desmethylzolmitriptan) were doubled. A maximum dose of 5mg Zomig Rapimelt 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). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

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 Pregnancy and lactation

Pregnancy

Zomig Rapimelt should be used in pregnancy only if the benefits to the mother justify potential risk to the foetus. There are no studies in pregnant women, but there is no evidence of teratogenicity in animal studies.

Lactation

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.

4.7 Effect on ability to drive and use machinery

There was no significant impairment of performance of psychomotor tests with doses up to 20 mg Zomig Rapimelt. Use is unlikely to result in an impairment of the ability of patients to drive or operate machinery. However it should be taken into account that somnolence may occur.

4.8 Undesirable effects

Zomig Rapimelt 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 incidences of ADRs associated with Zomig therapy are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

Frequency	System Organ Class	Event
Common (≥1% - <10%)	Gastrointestinal Disorders	Abdominal pain
		Dry Mouth
		Nausea
		Vomiting
		Dysphagia
	Musculoskeletal and Connective	Muscle weakness
	Tissue Disorders	Myalgia
	Nervous System Disorders	Abnormalities or disturbances of sensation
		Dizziness
		Headache
		Hyperaesthesia
		Paraesthesia
		Somnolence
		Warm sensation
	Cardiac Disorders	Palpitations
	General Disorders	Asthenia
		Heaviness, tightness, pain or pressure in throat,
		neck, limbs or chest

Table 1Table of Adverse Drug Reactions

Uncommon (≥0.1% - <1.0%)	Cardiac Disorders	Tachycardia
	Vascular Disorders	Transient increases in systemic blood
		pressure
	Renal and Urinary Disorders	Polyuria
		Increased urinary frequency
Rare (≥0.01% - <0.1%)	Immune System Disorders	Anaphylaxis/Anaphylactoid Reactions
		Hypersensitivity reactions
	Skin and Subcutaneous Tissue	Angioedema
	Disorders	Urticaria
Very rare (<0.01%)	Cardiac Disorders	Angina pectoris
-		Coronary Vasospasm
		Myocardial Infarction
	Gastrointestinal Disorders	Bloody diarrhoea
		Gastrointestinal infarction or necrosis
		Gastrointestinal ischaemic events
		Ischaemic colitis
		Splenic Infarction
	Renal and Urinary Disorders	Urinary urgency

4.9 Overdose

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

The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see Pharmacokinetic Properties section) and therefore monitoring of patients after overdose with Zomig Rapimelt 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

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 $5HT_{IB/1D}$ 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.

It has been demonstrated that the pain sensitive structures of the cranial cavity in humans are the blood vessels and the vasculature of the dura mater.

These tissues are innervated by trigeminal afferent fibres. In animal models the administration of zolmitriptan, with its agonist activity on the vascular $5HT_1$ receptors causes vasoconstriction associated with an inhibition of the release of calcitonin gene related peptide (CGRP), Vasoactive Intestinal Peptide (VIP) and substance P. These two events, vasoconstriction and inhibition of neuropeptide release are thought to cause relief from the migraine attack, as reflected by an onset of pain relief within 1 hour of administration and relief of nausea and vomiting, photophobia and phonophobia associated with migraine.

In addition to these peripheral actions, zolmitriptan has action on the central nervous system allowing access to both the peripheral and migraine centres in the brain stem which may explain the consistent effect over a series of attacks in a single patient. Vasodilatation is achieved with the activation of a reflex pathway mediated by trigeminal orthodromic fibres and parasympathetic innervation of the cerebral circulation via the release of VIP as a main effector transmitter. Zolmitriptan blocks this reflex pathway and the release of VIP.

5.2 Pharmacokinetic properties

Following oral administration of Zomig conventional tablets, zolmitriptan is rapidly and well absorbed (at least 64%). The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (N-desmethylzolmitriptan, the Ndesmethyl metabolite) which is also a $5HT_{1B/1D}$ agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan. 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. The Zomig Rapimelt orodispersible 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 orodispersible 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 the conventional tablet, and 1 to 6 hours (median 3.0 hours) for the orodispersible 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 orodispersible and conventional tablet formulations are similar up to 45 minutes post dose, the period of most importance for initial absorption following administration.

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 active whilst the others are not. 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. 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. Over 60% of a single oral dose is excreted in the urine (mainly as the indoleacetic 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% 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 third is renal clearance.

Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. The volume of distribution following iv 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 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 Zomig with ergotamine/caffeine was well tolerated and did not result in any increase in adverse events or blood pressure changes as compared to Zomig alone.

Selegiline, a MAO-B inhibitor, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), had no effect on the pharmacokinetic parameters of zolmitriptan.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 'Zomig Rapimelt' orodispersible tablet contains the following excipients:

Aspartame Citric Acid Anhydrous Silica Colloidal Anhydrous Crospovidone Magnesium Stearate Mannitol Microcrystalline Cellulose Orange Flavour SN027512 Sodium Hydrogen Carbonate

6.2 Shelf-life

Please refer to expiry date on the blister strip or outer carton.

6.3 Special precaution for storage

Do not store above 30°C.

6.4 Pack Size

Please refer to the outer carton for pack size. Not all presentations may be available locally.

6.5 Instructions for use

Zomig Rapimelt orodispersible tablets: The blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil). The Zomig Rapimelt tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva.

Product Owner

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