AUSTRALIAN PRODUCT INFORMATION

Zomig® and Zomig Rapimelt®
(zolmitriptan)

1 NAME OF THE MEDICINE

Zolmitriptan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zomig is presented as round, yellow (2.5 mg) or pink (5 mg), biconvex film-coated intagliated (with a 'Z' on one side) tablets containing 2.5 mg or 5 mg zolmitriptan.

The 2.5 mg tablets are 7.4 mm in diameter and are compressed to a weight of 122 mg. The 5 mg tablets are 8.6 mm in diameter and are compressed to a weight of 244 mg.

Zomig Rapimelt is presented as orally dispersible white round uncoated orange flavoured tablets containing 2.5 mg zolmitriptan. The tablets are 6.4 mm in diameter, flat-faced with a bevelled edge and intagliated with 'Z' on one side. The tablets are compressed to a weight of 100 mg.

Excipient(s) with known effect: lactose monohydrate (Zomig), aspartame (Zomig Rapimelt).

For the full list of excipients, see *Section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

- Tablet, film-coated
- Tablet, dispersible (oral)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The Zomig conventional tablet should be swallowed whole with water.

The 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 or have difficulty swallowing whole tablets.

If symptoms of migraine persist or recur within 24 hours of 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 achieve satisfactory relief with 2.5 mg doses, subsequent attacks can be treated with 5 mg doses of Zomig.

The onset of action in responders is apparent within 1 hour of dosing.

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

Zomig is not indicated for prophylaxis of migraine.

Patient subgroups

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

Paediatric use

The efficacy of Zomig tablets was not established in a placebo controlled clinical trial for patients aged 12 to 17 years. The efficacy and safety of Zomig in paediatric patients below 12 years have not been evaluated.

Use in the elderly

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

Use in adults with hepatic impairment

Although metabolism is reduced in patients with mild or moderate hepatic impairment (see Section 5.2 Pharmacokinetic properties), no dosage adjustment is required. However, for patients with severe hepatic impairment a maximum dose of 5 mg in 24 hours is recommended.

Use in adults with renal impairment

A study was carried out in patients with creatinine clearances from 5 to 39 mL/min. No dosage adjustment required (see Section 5.2 Pharmacokinetic properties).

Instructions for use/handling

Zomig tablets: No specific instructions.

Zomig Rapimelt orally dispersible 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to any component of the product.
- A history of myocardial infarction.
- Ischaemic heart disease; Prinzmetal angina/coronary vasospasm; peripheral vascular disease; symptoms or signs consistent with ischaemic heart disease.
- Moderate or severe hypertension and mild uncontrolled hypertension.
- Ergotamine or ergotamine derivatives should not be used concomitantly with Zomig.

- Other $5HT_{1D}$ receptor agonists should not be used concomitantly with Zomig.
- Creatinine clearance of less than 15 mL/min.
- On theoretical grounds (see Section 5.1 Pharmacodynamic properties / *Mechanism of action*), Zomig should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cerebrovascular events have been reported in patients treated with $5HT_1$ agonists, some resulting in fatalities. In a number of cases, it appears that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms were a consequence of the migraine. Zomig should only be used when 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 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 $5HT_1$ agonists.

There have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving Zomig.

Zomig should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

This class of compounds ($5HT_{1B/1D}$ agonists) has been associated with coronary vasospasm, angina pectoris and myocardial infarction. In very rare cases this has occurred with Zomig. In patients with risk factors for ischaemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including Zomig, is recommended (see Section 4.3 Contraindications). 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 $5HT_{1D}$ agonists, atypical sensations over the precordium (see Section 4.8 Adverse effects (Undesirable effects)) have been reported after the administration of zolmitriptan. Where such symptoms are thought to indicate ischaemic heart disease, no further doses of zolmitriptan should be given and appropriate evaluation carried out.

Serotonin Syndrome has been reported with combined use of triptans and other serotonergic medicines, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Noradrenaline Reuptake Inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition.

Signs and symptoms may include mental status changes (eg agitation, hallucinations, coma), autonomic instability (eg tachycardia, labile blood-pressure, hyperthermia), neuromuscular aberrations (eg hyperreflexia, in-coordination, weakness), and/or gastrointestinal symptoms (eg nausea, vomiting, diarrhoea).

In accordance with the Hunter Criteria, 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 when Zomig is administered with an SSRI or SNRI, particularly during treatment initiation and dosage increases (see Section 4.5 Interactions with other medicines and other forms of interactions).

Withdrawal of the serotonergic medicines usually brings about an improvement. Treatment depends on the type and severity of the symptoms.

Overuse of acute migraine medications may lead to exacerbations of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused medications, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Transient increases in systemic blood pressure (which may be more pronounced in the elderly) 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.

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

Use in adults with hepatic impairment

Although metabolism is reduced in patients with mild or moderate hepatic impairment (see Section 5.2 Pharmacokinetic properties), no dosage adjustment is required. However, for patients with severe hepatic impairment a maximum dose of 5 mg in 24 hours is recommended.

Use in adults with renal impairment

A study was carried out in patients with creatinine clearances from 5 to 39 mL/min. No dosage adjustment required (see Section 5.2 Pharmacokinetic properties).

Use in the elderly

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

Paediatric use

The efficacy of Zomig tablets was not established in a placebo controlled clinical trial for patients aged 12 to 17 years. The efficacy and safety of Zomig in paediatric patients below 12 years have not been evaluated.

Effects on laboratory tests

Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of Zomig (for example beta-blockers, oral dihydroergotamine, pizotifen).

The pharmacokinetics and tolerability of Zomig were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine. Concomitant administration of other $5HT_{1D}$ agonists within 24 hours of Zomig 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, and concomitant administration is contraindicated. 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 an ergotamine containing product.

The major metabolite of zolmitriptan, the indole acetic acid (2161W92), is derived from the active metabolite, N-desmethylzolmitriptan (183C91), by the action of monoamine oxidase A. This is evidenced by the effects of co-administration of the selective MAO-A inhibitor, moclobemide, which resulted in a 3-fold increase in the exposure to N-desmethylzolmitriptan but had minimal effects (increase of 26% in AUC) on zolmitriptan levels. (The metabolite N-desmethylzolmitriptan is also a $5HT_{1D}$ agonist with higher receptor affinity than the parent drug and therefore contributes to the overall effect after zolmitriptan administration). Hence, in patients taking a MAO-A inhibitor (selective or non-selective), a maximum intake of 5 mg Zomig in 24 hours is recommended.

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 5 mg Zomig 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.

Cases of life-threatening syndrome have been reported during combined use of triptans, and SSRIs (eg fluoxetine, fluvoxamine, paroxetine, sertraline) and SNRIs (eg venlafaxine) (see Section 4.4 Special warnings and precautions for use).

As with other $5HT_{1B/1D}$ agonists, there is a potential pharmacodynamic interaction 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

Effects on fertility

A fertility study by the oral route of administration, during which male and female rats were dosed daily with zolmitriptan prior to and throughout the mating period, showed no evidence of impaired fertility at doses producing plasma concentrations greater than 100 times those attained in humans after the maximum recommended daily dose of 10 mg (based on AUC).

Use in pregnancy – Category B3

There are no adequate and well-controlled studies in pregnant women. Studies in rats and rabbits treated with oral zolmitriptan during organogenesis, showed no direct teratogenic effects. Plasma concentrations in rats and rabbits receiving the highest doses were greater than 100 times and 40 times, respectively, the exposure (based on AUC) attained in humans after the maximum recommended daily dose of 10 mg. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Use in 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 to women who are breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even though there was no significant impairment of psychomotor test performances in healthy volunteers following doses of up to 20 mg, somnolence was reported in pharmacological and clinical trials. Caution is recommended in patients performing skilled tasks (eg driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack and following treatment.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Zomig is well tolerated. Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment. The adverse event profile is similar for both Zomig 2.5 mg and 5 mg tablets and for Zomig Rapimelt tablets.

Possible adverse reactions tend to occur within four hours of dosing and are no more frequent following repeated dosing; certain symptoms may be considered to be part of the migraine attack itself.

Clinical trial data

The incidence of adverse drug reactions associated with Zomig therapy is tabulated below according to the format recommended by the Council for International Organisations of Medical Sciences (CIOMS III working Group; 1995).

Table 1 Table of adverse drug reactions reported in Zomig clinical trials

Frequency	System Order Class	Event
Common (≥1% - <10%)	Nervous system disorders	Abnormalities or disturbances of sensation; dizziness; headache; hyperaesthesia; paraesthesia; somnolence; warm sensation
	Cardiac disorders	Palpitations
	Gastrointestinal disorders	Abdominal pain; dry mouth; nausea; vomiting; dysphagia
	Musculoskeletal & connective tissue disorders	Muscle weakness; myalgia
	General disorders	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest
Uncommon (≥0.1% - <1%)	Cardiac disorders	Tachycardia
	Vascular disorders	Transient increases in systemic blood pressure [a]
	Renal & urinary disorders	Polyuria; increased urinary frequency

Frequency	System Order Class	Event
Rare (≥0.01% - <0.1%)	Immune system disorders	Anaphylaxis/anaphylactoid reactions; hypersensitivity reactions
	Skin & subcutaneous disorders	Angioedema; 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 & urinary disorders	Urinary urgency

[a] May be more pronounced in the elderly; Reported in patients with and without a history of hypertension

Zomig (zolmitriptan) 2.5 mg and 5 mg tablets studies at the time of registration

Table 2 lists the adverse events that occurred in ≥2% of the patients in any one of the Zomig 2.5 mg, Zomig 5 mg or sumatriptan 100 mg dose groups of the controlled clinical trials. Only events that were more frequent in a treatment group compared to the placebo groups are included.

Table 2 Adverse experience incidence in five placebo-controlled migraine clinical trials: Events reported by ≥2% patients treated with Zomig or sumatriptan

Adverse event type	Placebo	Zomig 2.5 mg	Zomig 5 mg	Sumatriptan 100 mg
	(n=401)	(n=498)	(n=1012)	(n=504)
Atypical sensations	**7%**	**12%**	**17%**	**15%**
Hypaesthesia	1%	1%	2%	1%
Paraesthesia (all types)	2%	6%	8%	7%
Sensation warm/cold	4%	5%	7%	7%
Pain and pressure sensations	**7%**	**17%**	**25%**	**26%**
Chest – pain/tightness/pressure &/or heaviness	1%	3%	4%	5%
Neck/throat jaw – pain/tightness/pressure	3%	7%	10%	11%
Heaviness other than chest or neck	1%	2%	5%	5%
Pain - location specified	1%	2%	3%	1%
Other - Pressure/tightness	1%	3%	3%	4%
Digestive	**8%**	**16%**	**14%**	**14%**
Dry mouth	2%	3%	3%	2%
Dyspepsia	1%	2%	1%	1%
Dysphagia	0%	0%	2%	1%
Nausea	4%	9%	6%	7%
Neurological	**10%**	**17%**	**21%**	**18%**
Dizziness	4%	8%	10%	7%
Somnolence	3%	6%	8%	6%
Vertigo	0%	0%	2%	3%
Other				
Asthenia	3%	3%	9%	11%
Palpitations	1%	<1%	2%	2%
Myalgia	<1%	1%	2%	1%

Adverse event type	Placebo	Zomig 2.5 mg	Zomig 5 mg	Sumatriptan 100 mg
	(n=401)	(n=498)	(n=1012)	(n=504)
Myasthenia	<1%	1%	2%	1%
Sweating	1%	2%	3%	2%

Other adverse events reported less frequently are listed below; these are classified by body system categories and given in order of decreasing frequency, using the definitions: uncommon - occurring in 1/100 - 1/1,000 patients; rare - occurring in fewer than 1/1,000 patients. All reported events are included except those already listed in the table above, those too general to be informative and those not reasonably associated with the use of the drug.

Atypical sensation: Uncommon was hyperaesthesia of the mouth and skin.

General: Uncommon were allergy reaction, chills, facial oedema, fever, malaise and photosensitivity.

Cardiovascular: Uncommon were arrhythmias, hypertension and syncope. Rare were bradycardia, extrasystoles, postural hypotension, QT prolongation, tachycardia and thrombophlebitis.

Digestive: Uncommon were increased appetite, tongue oedema, esophagitis, gastroenteritis, liver function abnormality and thirst. Rare were anorexia, constipation, gastritis, haematemesis, pancreatitis, melena and ulcer.

Haemic: Uncommon was ecchymosis. Rare were cyanosis, thrombocytopenia, eosinophilia and leucopenia.

Metabolic: Uncommon was oedema. Rare were hyperglycemia and alkaline phosphatase increased.

Musculoskeletal: Uncommon were back pain, leg cramps and tenosynovitis. Rare were arthritis, tetany and twitching.

Neurological: Uncommon were agitation, anxiety, depression, emotional lability and insomnia; rare were akathisia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischaemia, hyperkinesia, hypotonia, hypertonia and irritability.

Respiratory: Uncommon were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis and yawn. Rare were apnoea and voice alteration.

Skin: Uncommon were pruritus, rash and urticaria.

Special senses: Uncommon were dry eye, eye pain, hyperacusis, ear pain, parosmia and tinnitus. Rare were diplopia and lacrimation.

Urogenital: Uncommon were haematuria, cystitis, polyuria, urinary frequency, urinary urgency. Rare were miscarriage and dysmenorrhoea.

Post-marketing data

See Section 4.8 Adverse effects (Undesirable effects)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 Pharmacokinetic properties) and therefore monitoring of patients after overdose with Zomig 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 $5HT_2$, $5HT_3$, $5HT_4$, α_1, α_2, or β_1, adrenergic; H_1, H_2, histaminic; muscarinic; dopaminergic$_1$, or dopaminergic$_2$ receptors. The N-desmethyl metabolite, N-desmethylzolmitriptan, is also a $5HT_{1B/1D}$ agonist and is 2 to 6 times more potent, in animal models, than zolmitriptan. This metabolite shows higher *in vitro* affinity for $5HT_{1B/1D}$ receptors than zolmitriptan and also has modest affinity for $5HT_{1A}$ 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 proposed 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, experimental studies in animals suggest 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. It is suggested that zolmitriptan blocks this reflex pathway and the release of VIP.

Clinical trials

Treatment of acute migraine, with or without aura, with Zomig 2.5 mg and 5 mg tablets

Overall there were 4003 unique individuals who participated in the zolmitriptan clinical development. A total of 3096 unique individuals were exposed to zolmitriptan. Of this total, 316 unique individuals were accounted for in Clinical Pharmacology studies; 2633 in placebo-controlled treatment of migraine studies, 79 in the long-term multiple attack study (Study 015; 2058 subjects in total, 79 of whom were unique subjects not previously exposed to zolmitriptan) 38 in two uncontrolled patient treatment studies; and 30 in an acute prevention of migraine study. In addition, 524 unique individuals were exposed to placebo (119 in clinical pharmacology studies, 401 in treatment of migraine studies).

These subjects received almost 50000 oral doses of zolmitriptan. Across all patient studies, a total of 34296 attacks were treated with zolmitriptan. The majority of these (31579) were treated in a long-term study.

In patient studies, the protocol inclusion criteria required patients to have an established diagnosis of migraine, with or without aura (as defined by the International Headache Society criteria). Patients had a migraine history of at least 1 year with an age of onset less than 50 years and had one to six migraines per month over the preceding 6 months. In addition, patients had to have screening laboratory values within acceptable ranges and be without evidence of ischaemic heart disease, arrhythmia, or accessory pathways, based on a 12-lead ECG. The age range of patients was 18-65 years in most studies.

The first of the pivotal studies was a Phase II study of almost 1200 patients comparing zolmitriptan (n=900) to placebo. The response rates at 2 hours in patients receiving placebo, zolmitriptan 5 mg, 10 mg, 15 mg and 20 mg were 21%, 61%, 67%, 67% and 74%, respectively. The response rate had been slightly lower at 1h post-dosing, being 16% in the group receiving placebo and 44-50% in the groups treated with zolmitriptan. The percentage of patients with no pain at 2 hours was 1% in the placebo group, and 39%, 39%, 43% and 47% in the zolmitriptan 5 mg, 10 mg, 15 mg and 20 mg groups, respectively. The placebo group also showed a far greater recurrence rate over 24 hours than the zolmitriptan groups, with median time to recurrence being 4.5 hours with placebo and 15.3 hours with zolmitriptan.

The incidence of adverse events was proportional to dose, and consisted predominantly of asthenia, heaviness (in the chest, limbs, head), nausea, paraesthesia, a feeling of warmth, dizziness, somnolence, vertigo and dry mouth. Of the cardiovascular events, 34 were noted with zolmitriptan versus 1 with placebo, but there was only 1 serious adverse event (tachycardia in a patient with a pre-existing condition of Wolff-Parkinson-White syndrome (see Section 4.4 Special warnings and precautions for use).

The phase III study also investigated approximately 1200 patients, but included lower doses of zolmitriptan (1 mg, 2.5 mg, 5 mg and 10 mg). The findings indicated that the response to zolmitriptan 1 mg was greater than the response to placebo, however no difference between placebo and zolmitriptan 1 mg was found in another study. The 2.5 mg dose was associated with a response rate of 63% versus 65% with the 5 mg dose, suggesting that these two dose levels were equi-effective. This study also showed the incidence of nausea to be reduced significantly with zolmitriptan treatment when compared with placebo. The safety profile of zolmitriptan was similar to that observed in the previous trials. There were no serious adverse events reported in this selected trial population.

Treatment of migraine, with or without aura with Zomig Rapimelt 2.5 mg tablets

The efficacy and tolerability of Zomig Rapimelt in the acute treatment of migraine headaches (with or without aura), as defined by the International Headache Society criteria was demonstrated in a large double-blind, placebo-controlled, parallel group clinical trial, involving 471 patients. Patients were randomised to receive either Zomig Rapimelt 2.5 mg (n=231) or placebo (n=240). For persistent or recurrent headaches, a second trial tablet or escape medication could be taken if required no sooner than two hours after the first dose. The primary end point was headache response at 2 hours, defined as a reduction in headache severity from moderate or severe pain to mild or no pain. Secondary endpoints were used to assess onset of action and included the proportion pain-free (no pain) at 30 minutes, 1, 2 and 4 hours; proportion with a one-point reduction in migraine headache rating scale at 30 minutes and 1 hour; subjective patient preference over conventional tablet; and adverse events.

The trial excluded patients with a history of basilar, ophthalmoplegic or hemiplegic migraine; a history or symptoms suggestive of ischaemic heart disease, other vascular disease, cardiac arrhythmias such as Wolff-Parkinson-White syndrome and conditions considered risk factors for ischaemic heart disease.

Both study groups were similar in terms of age, height, weight, race and migraine history (attacks/month over last 3 months; with or without aura; average duration and associated symptoms including nausea, photophobia, phonophobia and headache).

Zomig Rapimelt was superior to placebo in the relief of headache and associated symptoms of migraine during the four-hour measurement period. This effect was established one hour after ingestion and was maximal between 2 and 4 hours. Efficacy results for headache response are tabulated below for the intention to treat population.

Table 3 Headache response

	Response at 2 hours	**Response at 30 minutes***	**Response at 1 hour***	**Response at 4 hours***
Zomig Rapimelt	63% (n=220)	16% (n=227)	45% (n=224)	51% (n=226)
ZvsP (OR, 95% CI, p-value)	6.1 (4.0, 9.3) p < 0.0001	1.7 (1.0, 3.1) p=0.0538	3.5 (2.3, 5.3) p < 0.0001	6.3 (4.0, 9.8) p < 0.0001
Placebo	22% (n=236)	10% (n=237)	19% (n=232)	14% (n=239)

*Secondary efficacy parameters

More patients in the zolmitriptan group (40%) experienced a headache response through 24 hours after treatment with a single dose compared with patients in the placebo group (12%). The corresponding figures for patients achieving a pain-free state were 23% and 7%. Among those who used a second dose and/or escape medication, the median time to taking such a dose was 5 hours and 45 minutes following zolmitriptan and 2 hours and 109 minutes following placebo. From the Kaplan-Meier curve, 44% on zolmitriptan and 72% on placebo required rescue medication by 4 hours.

The percentage of patients with associated symptoms of nausea, photophobia and phonophobia were lower in the zolmitriptan group in the 4 hours following treatment. Subgroup analysis revealed a numerically greater response in those with moderate (as opposed to severe) headache and those without associated symptoms. In addition to producing a more significant reduction in headache and associated symptoms, zolmitriptan treatment was associated with a lower use of rescue medication compared with placebo.

The adverse event profile, including those affecting the upper gastrointestinal tract, for Zomig Rapimelt tablets was similar to that of zolmitriptan conventional tablets. The majority of adverse events were mild to moderate in intensity.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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% but there is some degree of intersubject variability.

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.

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.

Distribution

Plasma protein binding of zolmitriptan and the N-desmethyl metabolite is low (approximately 25%). The volume of distribution for the parent drug following i.v. administration is 2.4 L/kg.

Metabolism

Metabolism of zolmitriptan is dependent on CYP1A2 and the metabolism of the active metabolite N-desmethylzolmitriptan is via the monoamine oxidase A (MAO-A) 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 (N-desmethylzolmitriptan) is active whilst the others are not. 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.

Excretion

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. 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. The plasma half-life ($T_{½}$) of zolmitriptan was 4.7 hours in healthy volunteers. The corresponding $T_{½}$ values for the N-desmethylzolmitriptan metabolite was 5.7 hours. Following intravenous administration, the mean total plasma clearance is approximately 10 mL/min/kg, for the parent drug, of which one quarter is renal clearance. Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. . 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.

Special patient populations

Renal impairment

Renal clearance of zolmitriptan and 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.

Hepatic impairment

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 ($T_{½}$) of zolmitriptan was 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding $T_{½}$ values for the 183C91 metabolite were 7.5 hours and 7.8 hours respectively.

Use in the elderly

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

Pharmacokinetic interactions with other medicines

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.

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 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.

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

Zomig Rapimelt

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 the conventional tablet, and 1 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

Genotoxicity

Zolmitriptan showed no evidence of genotoxicity in a series of assays for gene mutations (bacteria and Chinese hamster ovary cells). Tests for chromosomal damage in human lymphocytes *in vitro,* showed that zolmitriptan was clastogenic, however, zolmitriptan was not clastogenic *in vivo*.

Carcinogenicity

In carcinogenicity studies, rats and mice were given zolmitriptan by oral gavage for 104 and 92 weeks, respectively. Average plasma concentrations in rats and mice receiving the highest doses were greater than 100 times the exposure (based on AUC) attained in humans after the maximum recommended daily dose of 10 mg. The rat study revealed an increased incidence of thyroid follicular cell adenoma at the highest dose tested, thought to be due to enhanced hepatic thyroxine clearance. There was no evidence of an increased incidence of tumours in the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Zomig film-coated tablets: Hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, macrogol (400 and 8000), sodium starch glycollate, titanium dioxide, iron oxide yellow CI 77492 (2.5 mg) and iron oxide red CI 77491 (5 mg).

Zomig Rapimelt: Aspartame, -microcrystalline cellulose, citric acid, crospovidone, magnesium stearate, mannitol, orange flavour SN027512, sodium bicarbonate and colloidal anhydrous silica.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Zomig 2.5 mg film-coated tablets: Store below 25°C.

Zomig 5 mg film-coated tablets and Zomig Rapimelt: Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Zomig 2.5 mg tablets: Presented in an aluminium laminate/aluminium foil blister pack containing 2, 3, 6 or 18 tablets. [1]

Zomig 5 mg tablets: Presented in an aluminium laminate/aluminium foil blister pack containing 2, 3, 6 or 18 tablets. [2]

Zomig Rapimelt tablets: Presented in a peelable aluminium laminate blister pack containing 2 or 6 tablets. [3]

1. Zomig 2.5 mg tablet is marketed in the 2-tablet foil blister pack in Australia, the 3, 6 and 18 tablet foil blister packs are not marketed in Australia.
2. Zomig 5 mg tablet is not marketed in Australia.
3. Zomig Rapimelt tablet is not marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

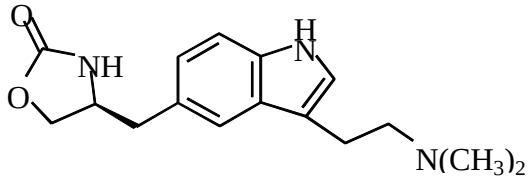
Zolmitriptan is a white to almost white powder slightly soluble in water (1.3 mg/mL at 250°C) but shows greater solubility in 0.1 M hydrochloric acid. Zolmitriptan has a pKa of 9.6. Zolmitriptan is a chiral molecule, which is synthesised as the S enantiomer.

Chemical structure

Chemical name: (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone (IUPAC)

The empirical formula is $C_{16}H_{21}N_3O_2$, representing a molecular weight of 287.36

Figure 1 Chemical structure of zolmitriptan



CAS number

139264-17-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

20 April 1998

10 DATE OF REVISION

03 August 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.4	Updated Storage Conditions for Zomig 2.5 film-coated tablets

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