# 1.5.5.2 FINAL PACKAGE INSERT

**SCHEDULING STATUS: S 4**

**PROPRIETARY NAME (and Dosage Form):**

**Zomig® 2,5; Zomig® 5; Zomig Rapimelt® (Tablet)**

**COMPOSITION:**

Each tablet contains 2,5 mg or 5 mg of zolmitriptan.

Contains sugar (lactose).

Each ZOMIG Rapimelt orodispersible tablet contains 2,5 mg of zolmitriptan.

The tablets are artificially sweetened with 5 mg of aspartame.

*List of excipients:*

*ZOMIG 2,5 and ZOMIG 5:*

Hypromellose, iron oxide (yellow – 2,5 mg tablet, red – 5 mg tablet), lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycollate and titanium dioxide.

*ZOMIG Rapimelt:*

Mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium hydrogen carbonate (sodium bicarbonate), citric acid anhydrous, silica colloidal anhydrous, orange flavour, magnesium stearate.

**PHARMACOLOGICAL CLASSIFICATION:**

A 7.3 Migraine preparations

**PHARMACOLOGICAL ACTION:**

*Pharmacodynamic properties:*

Zolmitriptan is 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.

In acute migraine, vasodilatation occurs with the activation of a reflex pathway mediated by trigeminal orthodromic fibres and parasympathetic innervation of the cerebral circulation via the release of vasoactive intestinal peptide (VIP) as a main effector transmitter. Zolmitriptan blocks this reflex pathway and the release of VIP.

*Pharmacokinetic properties:*

The mean absolute bioavailability of the parent compound is approximately 40 %.

In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite 183C91, display dose-proportional AUC and $C_{max}$ over the dose range 2,5-50 mg. Absorption

is rapid with 75 % of $C_{max}$ achieved within 1 hour and plasma concentrations are sustained subsequently for 4-6 hours. Zolmitriptan absorption is unaffected by the presence of food. There is no evidence of accumulation on multiple dosing of zolmitriptan. The ZOMIG Rapimelt orodispersible formulation has similar AUC and $C_{max}$ compared to the conventional formulation; but there is a significant delay in $T_{max}$ when compared to the conventional formulation, however there is no evidence that the delay in $T_{max}$ causes a delay in the onset of efficacy.

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. There are 3 major metabolites: the indole acetic acid (the major metabolite in plasma and urine), the N-oxide and N-desmethyl analogues. The N-desmethylated metabolite (183C91) is active whilst the others are not. Plasma concentrations of 183C91 are approximately half those of the parent compound. 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 oral 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-desmethyl zolmitriptan 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 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 $t_{½}$ values for the N-desmethyl zolmitriptan 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 litres/kg. Plasma protein binding is low (approximately 25 %). The mean elimination half-life of zolmitriptan is 2,5-3 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 3-3,5 hours. These parameters are within the ranges seen in healthy volunteers.

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

**INDICATIONS:**

ZOMIG is indicated for the acute treatment of migraine with or without aura in adults.

**CONTRAINDICATIONS:**

ZOMIG is contraindicated in patients with known hypersensitivity to any component of the product.

ZOMIG must not be given to patients with severe hypertension.

Ischaemic heart disease.

Coronary vasospasm/Prinzmetal's angina.

Moderate to severe hepatic impairment.

**WARNINGS:**

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

ZOMIG 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 ZOMIG, is recommended (see

"*Contraindications*"). These evaluations, however, may not identify every patient who has cardiac disease and serious cardiac events have occurred in patients without underlying cardiovascular disease.

Patients with phenylketonuria should be informed that ZOMIG Rapimelt orodispersible tablets contain phenylalanine (a component of aspartame). Each 2,5 mg orodispersible tablet contains 2,81 mg of phenylalanine.

The serotonin syndrome has been reported with combined use of triptans such as ZOMIG, and selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Serotonin syndrome is a potentially life-threatening condition, and it may include signs and symptoms such as mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood-pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, in-coordination), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Careful observation of the patient is advised, if concomitant treatment with ZOMIG and SSRI or SNRI, particularly during treatment initiation and dosage increases (see "*Interactions*").

*Use in patients aged over 65 years:*

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

*Patients with hepatic impairment:*

Although zolmitriptan metabolism is reduced in patients with hepatic impairment, no dosage adjustment is required for patients with mild hepatic impairment. A maximum dose of 5 mg of ZOMIG in 24 hours is recommended.

*Patients with renal impairment:*

No dosage adjustment required (see "*Pharmacokinetic properties*").

**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 $5HT_{1B/1D}$ agonists within 12 hours of ZOMIG treatment should be avoided.

Ergot-containing medicines have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, 24 hours should elapse between the use of ergotamine containing or ergot-type medications (like dihydroergotamine or methysergide) and ZOMIG.

Conversely, it is advised to wait at least 6 hours following the use of ZOMIG before administering an ergotamine containing preparation.

In a small group of healthy individuals there was no pharmacokinetic interaction with ergotamine. Concomitant administration of ZOMIG with ergotamine/caffeine did not result in any increase in adverse events or blood pressure changes as compared with ZOMIG alone.

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

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 an MAO-A inhibitor.

Following the administration of cimetidine, a general P450 inhibitor, the half-lives of zolmitriptan and the active metabolite were significantly increased. 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 (e.g. 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 serotonin syndrome have been reported during combined use of triptans, and selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, sertraline) and serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine, duloxetine) (see "*Warnings*").

**PREGNANCY AND LACTATION:**

*Pregnancy:*

Safety in pregnancy and lactation has not been established.

*Lactation:*

ZOMIG is not recommended for women who are breastfeeding.

**DOSAGE AND DIRECTIONS FOR USE:**

The recommended dose of ZOMIG to treat a migraine attack is 2,5 mg.

If a patient does not achieve satisfactory relief with 2,5 mg doses, subsequent attacks can be treated with 5 mg doses of ZOMIG.

ZOMIG is effective whenever the tablets are taken during a migraine attack; although it is advisable that the ZOMIG tablets are taken as early as possible after the onset of migraine headache.

The ZOMIG conventional tablet should be swallowed whole with water.

ZOMIG Rapimelt orodispersible tablets can be taken when water is not available or by patients who suffer from nausea and are unable to drink during a migraine attack.

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.

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.

In those patients who respond, statistically significant efficacy is apparent within 1 hour of dosing.

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.

*Use in patient subgroups:*

*Use in adolescents and children (under 18 years):*

Safety and efficacy have not been established. Use of ZOMIG in adolescents and children is therefore not recommended.

The efficacy and safety of ZOMIG in paediatric patients below 12 years have not been evaluated.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS:**

*Side-Effects:*

Possible adverse reactions tend to occur within 4 hours of dosing and are no more frequent following repeated dosing.

| Frequency | System Organ Class | Event |
|---|---|---|
| Common (≥ 1 % - < 10 %) | Nervous system disorders | Abnormalities or disturbances of sensation, Dizziness, Paraesthesia, Somnolence, Warm sensation, Headache |
| | Cardiac disorders | Palpitations |
| | Gastrointestinal disorders | Dry mouth, Nausea, Vomiting, Dysphagia, Dyspepsia, Abdominal pain |
| | Musculoskeletal and connective tissue disorders | Muscle weakness, Myalgia |

| Frequency | System Organ Class | Event |
|---|---|---|
| | 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 |
| | Renal urinary disorders | Polyuria, Increased urinary frequency |
| Rare (≥ 0,01 % - < 0,1 %) | Immune system disorders | Anaphylaxis/Anaphylactoid reactions, Hypersensitivity reactions |
| | Skin and subcutaneous tissue 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 and urinary disorders | Urinary urgency |

*Special Precautions:*

ZOMIG 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 in hemiplegic or basilar migraine. Migraineurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with ZOMIG. Atypical sensations over the precordium have been reported after the administration of ZOMIG. Where such symptoms are thought to indicate ischaemic heart disease, no further doses of ZOMIG should be given and appropriate evaluation carried out.

ZOMIG film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take ZOMIG.

*Effects on ability to drive and use machines:*

There was no statistically significant impairment of performance of psychomotor tests with doses up to 20 mg ZOMIG. However, it should be taken into account that somnolence may occur.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

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

The elimination half-life of zolmitriptan administration is approximately 3 hours 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.

**IDENTIFICATION:**

*ZOMIG 2,5:*

Round, biconvex, yellow film-coated tablets. The tablets are plain on one side and intagliated with a 'Z' on the other side.

*ZOMIG 5:*

Round, biconvex, pink film-coated tablets. The tablets are plain on one side and intagliated with a 'Z' on the other side.

*ZOMIG Rapimelt:*

White, flat faced, round, bevelled edge tablet, intagliated with letter 'Z' on one side.

**PRESENTATION:**

ZOMIG 2,5 mg and 5 mg tablets are available in blister packs of 6 or 18 tablets.

ZOMIG Rapimelt orodispersible tablets are available in aluminium blister packs of 6 tablets.

**STORAGE INSTRUCTIONS:**

Store at or below 30 °C. Keep out of reach of children.

**REGISTRATION NUMBERS:**

ZOMIG 2,5: 32/7.3/0478

ZOMIG 5: 32/7.3/0479

ZOMIG Rapimelt: 34/7.3/0107

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

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AstraZeneca Logo

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