

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Zomig™ 2.5 mg film-coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zolmitriptan

Each 2.5 mg film-coated tablet contains 2.5 mg zolmitriptan

Excipients:

Each 2.5 mg film-coated tablet contains 100 mg lactose

For a full list of excipients, see section 6.1

### 3. PHARMACEUTICAL FORM

Film-coated tablet

Round, biconvex, yellow film-coated tablets containing 2.5 mg of zolmitriptan. The tablets are intagliated with the letter 'Z' on one side.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Acute treatment of migraine headache with or without aura.

#### 4.2 Posology and method of administration

The recommended dose of 'Zomig' tablets to treat a migraine attack is 2.5 mg. It is advisable that 'Zomig' tablets are taken as early as possible after the onset of migraine headache but they are also effective if taken at a later stage.

The tablets should be swallowed whole and with water.

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' could be considered.

The total daily intake should not exceed 10 mg. Not more than 2 doses of 'Zomig' should be taken in any 24 hour period.

'Zomig' is not indicated for prophylaxis of migraine.

### **Use in Children (under 12 years of age)**

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

### **Use in patients aged over 65 years**

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

### **Patients with 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.

### **Patients with 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).

### **Interactions requiring dose adjustment (see Section 4.5)**

For patients taking MAO-A inhibitors, a maximum dose of 5 mg in 24 hours is recommended.

A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking cimetidine.

A maximum dose of 5 mg zolmitriptan in 24 hours is recommended in patients taking specific inhibitors of CYP 1A2 such as fluvoxamine and the quinolones (eg ciprofloxacin).

## **4.3 Contraindications**

'Zomig' is contraindicated in patients with known hypersensitivity to zolmitriptan or to any of the excipients.

Moderate or severe hypertension, and mild uncontrolled hypertension.

This class of compounds (5HT<sub>1B/1D</sub> receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore 'Zomig' 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, ergotamine derivatives (including methysergide), sumatriptan, naratriptan and other 5HT<sub>1B/1D</sub> receptor agonists with zolmitriptan is contraindicated (see Section 4.5).

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

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

#### **4.4 Special warnings and special precautions for use**

Zolmitriptan 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. Zolmitriptan is not indicated for use in hemiplegic, basilar or ophthalmoplegic migraine. Stroke and other cerebrovascular events have been reported in patients treated with 5HT<sub>1B/1D</sub> agonists. It should be noted that migraineurs may be at risk of certain cerebrovascular events.

Zolmitriptan 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<sub>1B/1D</sub> agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. 'Zomig' should not be given to patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus, heredity) without prior cardiovascular evaluation (see Section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. 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<sub>1B/1D</sub> receptor agonists, heaviness, pressure or tightness over the precordium (See Section 4.8) have been reported after the administration of zolmitriptan. If chest pain or symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be taken until after appropriate medical evaluation has been carried out.

As with other 5HT<sub>1B/1D</sub> 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.

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  $>38^{\circ}\text{C}$  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.

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with zolmitriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see section 4.5).

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **4.5 Interactions 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 zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering an ergotamine containing product (see section 4.3).

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the

active metabolite. Therefore, a maximum intake of 5 mg zolmitriptan in 24 hours, is recommended in patients taking a MAO-A inhibitor. The medicinal products should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

Following the administration of cimetidine, a general P<sub>450</sub> 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 zolmitriptan 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 (eg ciprofloxacin).

Selegiline (a MAO-B inhibitor) and fluoxetine (an SSRI) did not result in any pharmacokinetic interaction with zolmitriptan. However, there have been reports describing patients with symptoms compatible with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see section 4.4). As with other 5HT<sub>1B/1D</sub> receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

Concomitant administration of other 5HT<sub>1B/1D</sub> agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other 5HT<sub>1B/1D</sub> agonists should be avoided.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (*Hypericum perforatum*).

## **4.6 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.

### **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 zolmitriptan 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 (eg driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack.

#### 4.8 Undesirable effects

Possible undesirable effects are typically transient, tend to occur within four hours of dosing, are no more frequent following repeated dosing and resolve spontaneously without additional treatment.

The following definitions apply to the incidence of the undesirable effects:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100, < 1/10$ ); uncommon ( $\geq 1/1000, < 1/100$ ), rare ( $\geq 1/10000, < 1/1000$ ), very rare ( $< 1/10000$ ).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects have been reported following administration of zolmitriptan:

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions
Nervous system disorders	Common	Abnormalities or disturbances or sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Myocardial infarction; Angina pectoris; Coronary vasospasm
Vascular disorders	Uncommon	Slight increases in blood pressure; Transient increases in systemic blood pressure
Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth

System Organ Class	Frequency	Undesirable Effect
	Very rare	Ischaemia or infarction (e.g. intestinal ischaemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain
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 disorders	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 is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475 Nicosia, tel: +357 22608607, Fax: + 357 22608669, website: [www.moh.gov.cy/phs](http://www.moh.gov.cy/phs)

#### **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) 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.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Selective serotonin (5HT<sub>1</sub>) agonists.  
ATC code: N02CC03

Zolmitriptan has been demonstrated to be a selective agonist for 5-HT<sub>1B/1D</sub> receptors mediating vascular contraction. Zolmitriptan has high affinity for human recombinant 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors, and modest affinity for 5-HT<sub>1A</sub> receptors. Zolmitriptan has no significant affinity or pharmacological activity at other 5-HT receptor subtypes (5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>) or adrenergic, histaminic, muscarinic or dopaminergic 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 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 is consistently effective in migraine with or without aura and in menstrually associated migraine. Zolmitriptan, if taken during the aura, has not been demonstrated to prevent the migraine headache and therefore 'Zomig' should be taken during the headache phase of migraine.

One controlled clinical trial in 696 adolescents with migraine failed to demonstrate superiority of zolmitriptan tablets at doses of 2.5mg, 5mg and 10mg over placebo. Efficacy was not demonstrated.

## **5.2 Pharmacokinetic properties**

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) Zolmitriptan is metabolised by CYP1A2, forming N-desmethylzolmitriptan, which is also a 5HT<sub>1B/1D</sub> receptor 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.

In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite, the N-desmethyl metabolite, display dose-proportional AUC and C<sub>max</sub> over the dose range 2.5 to 50 mg. Absorption of zolmitriptan is rapid. In healthy volunteers, 75% of C<sub>max</sub> is achieved within 1 hour, and after this the concentration of zolmitriptan in plasma is maintained at approximately this level until 4-5 hours after dosing. 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. 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.

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 iv 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 an 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<sub>max</sub> were increased by 226% and 50%, respectively and the half life was prolonged to 12 h in subjects with severe liver disease compared to healthy subjects. Exposure to the metabolites, including the active metabolite was reduced.

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

### **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<sub>1B/1D</sub> receptor agonists, zolmitriptan binds to melanin.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose anhydrate  
Microcrystalline Cellulose  
Sodium Starch Glycollate (Type A)  
Magnesium Stearate  
Hypromellose  
Macrogol (400 and 8000)  
Iron oxide (E172: yellow)  
Titanium dioxide (E171)

## **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 of 2.5 in blister packs, containing 3 or 6 tablets.  
The blister strip is polyamide Al-PVC/Al.  
Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

No special requirements

## **7 MARKETING AUTHORISATION HOLDER**

C.G. Papaloisou Ltd,  
35 Kilkis Avenue, 2234 Cyprus

## **8 MARKETING AUTHORISATION NUMBER(S)**

Zomig<sup>TM</sup> 2.5 mg : 17688

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**

13 April 1998

## **10 DATE OF REVISION OF THE TEXT**

6/06/2022