SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zomig 2.5 mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of zolmitriptan.

Excipient(s) with known effect

Each tablet contains 100 mg lactose anhydrous.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

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.

In those patients who respond, significant efficacy 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 is 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.

Paediatric population (under 12 years of age)

The safety and efficacy of Zomig tablets in children aged 0-12 years has not yet been established. No data are available. 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.

Elderly

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

Hepatic impairment

Metabolism is reduced in patients with hepatic impairment (see Section 5.2). Therefore for patients with moderate or severe hepatic impairment a maximum dose of 5 mg in 24 hours is recommended.

Renal impairment

No dosage adjustment required (see Section 5.2).

Method of administration

To be taken by oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Uncontrolled hypertension.
- Ischaemic heart disease.
- Coronary vasospasm/Prinzmetal's angina
- Peripheral vascular disease (PVD)
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Concomitant administration of Zomig with ergotamine or ergotamine derivatives or other 5-HT_1 receptor agonists.

4.4 Special warnings and precautions for use

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 $5HT_{1B/1D}$ agonists.

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

In very rare cases, as with other $5HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. In patients with risk factors for ischaemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including Zomig, is recommended (see Section 4.3). 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 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 $5HT_{1B/1D}$ 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.

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.

Serotonin Syndrome has been reported with combined use of triptans, and serotonergic drugs, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition, and diagnosis is likely when (in presence of a serotonergic agent) one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and inducible or ocular clonus.

Careful observation of the patient is advised, if concomitant treatment with Zomig and an SSRI or SNRI is clinically warranted, 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.

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

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

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 (for example beta blockers, oral dihydroergotamine, and 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 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. 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 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 Zomig in 24 hours is recommended in patients taking an 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 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).

Fluoxetine does not affect the pharmacokinetic parameters of zolmitriptan. Therapeutic doses of the specific serotonin reuptake inhibitors, fluoxetine, sertraline, paroxetine and citalopram do not inhibit CYP1A2. However, Serotonin Syndrome has been reported during combined use of triptans, and SSRIs (e.g. fluoxetine, paroxetine, sertraline) and SNRIs (e.g. venlafaxine, duloxetine) (see Section 4.4).

As with other $5HT_{IB/ID}$ 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 Fertility, Pregnancy and lactation

Pregnancy

Zomig 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 (see Section 5.3).

Breast-feeding

Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be exercised when administering Zomig to women who are breast-feeding.

4.7 Effects on ability to drive and use machines

There was no significant impairment of performance of psychomotor tests with doses up to 20 mg Zomig. Zomig has no or negligible influence on the ability to drive and use machines. However it should be taken into account that somnolence may occur.

4.8 Undesirable effects

Summary of the safety profile

Zomig 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. Tabulated list of adverse reactions

Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to < 1/10), Uncommon (≥1/1,000 to < 1/100), Rare (≥1/10,000 to < 1/1,000), Very rare (<1/10,000).

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

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Anaphylaxis/Anaphylactoid Reactions; Hypersensitivity reactions.
Nervous system disorder	Common	Abnormalities or disturbances of sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation.
Cardiac disorders	Common	Palpitations.
	Uncommon	Tachycardia.
	Very rare	Angina pectoris; Coronary vasospasm; Myocardial infarction.
Vascular disorders	Uncommon	Transient increases in systemic blood pressure

Gastrointestinal disorders	Common	Abdominal pain; Dry mouth; Nausea; Vomiting Dysphagia.
	Very rare	Bloody diarrhoea; Gastrointestinal infarction or necrosis; Gastrointestinal ischaemic events; Ischaemic colitis; Splenic infarction.
Skin and subcutaneous tissue disorders	Rare	Angioedema; Urticaria.
Musculoskeletal and connective tissue disorders	Common	Muscle weakness; Myalgia.
Renal and urinary disorders	Uncommon	Polyuria; Increased urinary frequency
	Very rare	Urinary urgency.

General disorders and administration site conditions	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Symptoms

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

Management

The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see Section 5.2) and therefore monitoring of patients after overdose with Zomig 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 ($5HT_1$) agonists, ATC code: N02CC03

Mechanism of action

In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant $5HT_{1B}$ and $5HT_{1D}$ receptor subtypes. Zolmitriptan is a high affinity $5HT_{1B/1D}$ receptor agonist with modest affinity for $5HT_{1A}$ receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at $5HT_2$-, $5HT_3$-, $5HT_4$-, $alpha_1$-, $alpha_2$-, 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 and preclinical studies have shown that zolmitriptan is able to act at both these sites.

Clinical efficacy and safety

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

5.2 Pharmacokinetic properties

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 (N-desmethylzomitriptan) which is also a $5HT_{1B/1D}$ agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan.

In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite 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.

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 pharmacologically active whilst the others are not. Zolmitriptan is metabolised by CYP1A2, forming N-desmethylzolmitriptan. The active metabolite is then further metabolised through MAO-A enzyme system. Plasma concentrations of the N-desmethylated metabolite are approximately half those of the parent drug, hence it would therefore be expected to contribute to the therapeutic action of Zomig. Over 60% of a single oral dose is excreted in the urine (mainly as the indole acetic acid metabolite) and about 30% in faeces, mainly as unchanged parent compound.

A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and C_{max} were increased by 94% and 50% respectively in patients with moderate liver disease and by 226% and 47% in patients with severe liver disease compared with healthy volunteers. Exposure to the metabolites, including the active metabolite, was decreased. For the active metabolite (N-desmethylzolmitriptan), AUC and Cmax 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 (T½) 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 T½ 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 intravenous 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.

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 with Zomig alone (see Section 4.5).

Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Selegiline, an MAO-B inhibitor, and fluoxetine (a selective serotonin reuptake inhibitor; SSRI) had no effect on the pharmacokinetic parameters of zolmitriptan (see Section 4.4).

Renal impairment

Renal clearance of zolmitriptan and all 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.

Elderly

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

5.3 Preclinical safety data

An oral teratology study of 'Zomig' has been conducted. At the maximum tolerated doses of 'Zomig', 1200 mg/kg/day (AUC 605 μg/ml.h: approx. 3700 x AUC of the human maximum recommended daily intake of 15 mg) and 30 mg/kg/day (AUC 4.9 μg/ml.h: approx. 30 x AUC of the human maximum recommended daily intake of 15 mg) in rats and rabbits, respectively, no signs of teratogenicity were apparent.

Five genotoxicity tests have been performed. It was concluded that 'Zomig' is not likely to pose any genetic risk in humans.

Carcinogenicity studies in rats and mice were conducted at the highest feasible doses and gave no suggestion of tumorogenicity.

Reproductive studies in male and female rats, at dose levels limited by toxicity, revealed no effect on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are contained in each tablet as indicated:

Lactose anhydrous
Microcrystalline cellulose
Sodium starch glycollate type A
Magnesium stearate
yellow color concentrate OY-22906 (Opadry)

Polyethylene glycol (8000)
Hydroxypropyl methylcellulose
Titanium dioxide

Polyethylene glycol (400)
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Packs of 2, 3, 6 and 18 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION NUMBER

108 67 29181 00

8. Manufacturer

Farmaceutici Formenti S.p.A, Italy

9. LICENSE HOLDER AND IMPORTER

AstraZeneca Israel Ltd.
1 Atirei Yeda St., Kfar Saba, 4464301.

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