Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zomig 2.5mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Zolmitriptan 2.5 mg

Also contains lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Product imported from the UK:
Yellow, round tablets and marked 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’ 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 2.5mg 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 paedriatic 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 'Zomig' 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 Contraindications and Section 5.2 Pharmacokinetic Properties)*

4.3 Contraindications

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

Moderate or severe hypertension, and uncontrolled hypertension.

This class of compounds ($5HT_{1B/1D}$ 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, derivatives of ergotamine (including methysergide), sumatriptan, naratriptan and other $5HT_{1B/1D}$ receptor agonists with 'Zomig' is contraindicated *(see Interactions Section 4.5).*

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

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

4.4 Special warnings and precautions for use

'Zomig' 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. 'Zomig' is not indicated for use in hemiplegic, basilar or ophthalmophlegic migraine. Migraneurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with $5HT_{1B/1D}$ agonists.

'Zomig' 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 compound, including 'Zomig', is recommended (see Section 4.3 contraindications). Such patients include postmenopausal women, males over 40 and patients with risk factors for coronary artery disease.

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 $5HT_{1B/1D}$ receptor agonists, heaviness, pressure or tightness over the precordium (See Undesirable effects Section 4.8)) have been reported after the administration of zolmitriptan.

If symptoms consistent with ischaemic heart disease occur, no further doses of zolmitriptan should be given and appropriate evaluation should be 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.

The dose recommendation for zolmitriptan should not be exceeded.

As with other $5HT_{1B/1D}$ agonists, there have been rare reports of anaphylaxis/ anaphylactoid reactions in patients receiving Zomig.

Serotonin Syndrome has been reported with combined use of triptans, 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 an SSRI or SNRI is necessary particularly during treatment initiation and dosage increases (See 4.5).

Undesirable effects may be more common during concomitant use of Zomig and herbal preparations containing St John's wort.
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 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 Interaction 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 '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 *(see Contraindications 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 a MAO-A inhibitor. The drugs 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 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 (183C91) were doubled. A maximum dose of 5mg '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 CYP 1A2 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.

Selegiline (a MAO-B inhibitor) and fluoxetine (an SSRI) did not result in any pharmacokinetic interaction with zolmitriptan. However, Serotonin Syndrome has been reported with combined use of triptans, and SSRIs (e.g. fluoxetine, paroxetine, sertraline) and SNRIs (e.g. venlafaxine, duloxetine) *(See 4.4).*

As with other $5HT_{1B/1D}$ receptor agonists, 'Zomig' could delay the absorption of other drugs.

4.6 Fertility, 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 'Zomig' 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 'Zomig'. 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

Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment. Possible adverse reactions tend to occur within four hours of dosing and are no more frequent following repeated dosing.

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

Very common (≥1/10); common (≥1/100 < 1/10); uncommon (≥1/1,000 < 1/100); rare (≥1/10,000 < 1/1,000); very rare (<1/10,000).

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

Table 1 Table of Adverse Drug Reactions

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
	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	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest

Certain symptoms, may be part of the migraine attack itself.

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 Pharmacokinetic Properties 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

In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant $5HT_{IB}$ and $5HT_{ID}$ receptor subtypes. Zolmitriptan is a high affinity $5HT_{1B/1D}$ receptor agonist with modest affinity for $5HT_{IA}$ 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.

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.

'Zomig' is consistently effective in migraine with or without aura and in menstrually associated migraine. 'Zomig', 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 2.5 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 (the N-desmethyl metabolite) which is also a $5HT_{1B/1D}$ receptor 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, the N-desmethyl metabolite, 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 in healthy volunteers and plasma concentrations are sustained subsequently for 4 to 6 hours. 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.

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 183C91 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 (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 183C91 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 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 a 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_{max} 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.

Selegiline, a MAO-B inhibitor, and fluoxetine had no effect on the pharmacokinetic parameters of zolmitriptan (see section 4.4 for warnings and precautions regarding concomitant use with SSRIs).

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 $5HT_{1B/1D}$ receptor agonists, zolmitriptan binds to melanin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are contained in each tablet as indicated:

Hypromellose
Lactose
Magnesium stearate
Microcrystalline cellulose
Macrogol (400 and 8000)
Sodium starch glycolate

Titanium dioxide (E171)
Iron oxide (E172: yellow)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Tablets in blister packs containing 6 tablets (with wallet). In an over-labelled outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

IPS Healthcare Limited
Sterling House
501 Middleton Road
Chadderton
Oldham, Lancashire OL9 9LY
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1659/38/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd July 2011

10 DATE OF REVISION OF THE TEXT