IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1473/039/002
Case No: 2071280

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Zomig Rapimelt 2.5mg Orodispersible Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/02/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zomig Rapimelt 2.5mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oro-dispersible tablet contains Zolmitriptan 2.5mg.

Excipients: Also includes aspartame (E951).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oro-dispersible tablets

Product imported from the UK:
Round, white uncoated orodispersible tablets impressed with ‘Z’ on one side with a beveled edge.

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 Rapimelt’ to treat a migraine attack is 2.5 mg. It is advisable that ‘Zomig Rapimelt’ orally dispersible 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 ‘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.

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 Rapimelt’ could be considered.

The total daily intake should not exceed 10 mg. Not more than 2 doses of ‘Zomig Rapimelt’ should be taken in any 24 hour period.
‘Zomig Rapimelt’ 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 Rapimelt 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 Rapimelt 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 evaluated. Use of 'Zomig Rapimelt' 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 Rapimelt' is contraindicated in patients with known hypersensitivity to any component of the product.

Moderate or severe hypertension, and mild uncontrolled hypertension.

This class of compounds ($5HT_{1D/IB}$ receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore 'Zomig Rapimelt' 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 Rapimelt" should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

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

4.4 Special warnings and precautions for use

'Zomig Rapimelt' 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 Rapimelt' is not indicated for use in hemiplegic, basilar or ophthalmophlegic 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 Rapimelt' 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. hyperrflexia, 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, 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.

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.

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.

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 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 'Zomig Rapimelt'. Conversely it is advised to wait at least six hours following use of 'Zomig Rapimelt' 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 Rapimelt' 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 administration of cimetidine, a general P_{450} inhibitor, the half life and AUC of zolmitriptan and its active metabolite were approximately doubled. A maximum dose of 5 mg 'Zomig Rapimelt' 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). 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, zolmitriptan could delay the absorption of other drugs.

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 'Zomig Rapimelt' 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

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 incidences of ADRs associated with Zomig therapy are tabulated below according to the format recommended by the Council for International Organisations of Medical Sciences (CIOMS III Working Group; 1995).

Common (≥ 1% - < 10%)	
Nervous Disorders:	Abnormailites or disturbances of sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac Disorders:	Palpitations
Gastrointestinal Disorders:	Abdominal Pain; Nausea; Dry mouth; Vomiting

Musculoskeletal and Connective Tissue Disorders:	Muscle weakness; Myalgia
General Disorders:	Asthenia; Heaviness in limbs, chest and neck; Tightness in throat, neck, limbs and chest; Pain or pressure in throat, jaw, neck and chest
Uncommon (>0.1%-<1.0%)	
Cardiac Disorders:	Tachycardia
Vascular Disorders:	Transient increase in systemic blood pressure
Renal and 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; Ischeamic colitis; Splenic Infarction
Renal Urinary Disorders:	Urinary Ugency

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 Rapimelt’ orally dispersible 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

ATC Classification: 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 with 'Zomig' conventional tablets 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, when administered as conventional oral tablets, is consistently effective in migraine with or without aura and in menstrually associated migraine. Zolmitriptan, when administered as conventional oral tablets, if taken during the aura, has not been demonstrated to prevent the migraine headache and therefore 'Zomig Rapimelt' 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

Following oral administration of 'Zomig' conventional tablets, 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 Cmax 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 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 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 Cmax 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.

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

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 (183C91). The time to maximum plasma concentration following administration of ‘Zomig

Rapimelt’ is similar for the active metabolite (183C91) 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 183C91, the t_{max} ranged from 0.75 to 5 hours (median 3.0 hours) for conventional tablet, and 1.0 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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Anhydrous citric acid
Silica, colloidal anhydrous
Crospovidone
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Orange Flavour – SN027512
Sodium hydrogen carbonate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the over-labelled outer container and on the blister foils of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Keep your medicine in the container it came in.

6.5 Nature and contents of container

Tablets in peelable aluminium laminate 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

The blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil).

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals
4 Altona Road
Lisburn
Co. Down
BT27 5QB
N. Ireland

8 Parallel Product Authorisation Number

PPA1473/39/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th February 2010

10 DATE OF REVISION OF THE TEXT