IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1380/035/004
Case No: 2047094

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

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

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

Zolmiles 5 mg 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 **14/08/2009** until **13/08/2014**.

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

Zolmiles 5 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mg orodispersible tablet contains 5 mg zolmitriptan.

Excipient:
Each 5 mg orodispersible tablet contains 8 mg aspartame.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

White and round flat tablets with the diameter 9.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute treatment of migraine headache with or without aura.

4.2 Posology and method of administration

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

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

The tablet need not be taken with liquid; the tablet dissolves on the tongue and is swallowed with saliva. This formulation can be used in situations in which liquids are not available, or to avoid the nausea and vomiting that may accompany the ingestion of tablets with liquids. However, a delay in the absorption of zolmitriptan from the dispersible tablet can occur which may delay onset of action.
The blister pack should be peeled open (tablets should not be pushed through the foil). The tablet should be placed on the tongue, where it will dissolve and be swallowed with the saliva.

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 zolmitriptan could be considered.

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

Zolmitriptan is not indicated for prophylaxis of migraine.

Use in Children (below 12 years of age)
Safety and efficacy of zolmitriptan tablets in paediatric patients have not been evaluated. Use of zolmitriptan in children is therefore not recommended.

Adolescents (12 - 17 years of age)
The efficacy of zolmitriptan tablets was not demonstrated in a placebo controlled clinical trial for patients aged 12 to 17 years. Use of zolmitriptan 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 zolmitriptan 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 (e.g. ciprofloxacin).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Moderate or severe hypertension, and mild 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 Zolmiles 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 zolmitriptan is contraindicated (see Interactions 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 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 $5HT_{1B/1D}$ agonists. It should be noted that migraneurs 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 $5HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. Zolmiles 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 $5HT_{1B/1D}$ 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 $5HT_{1B/1D}$ 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.

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

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.

Zolmiles contains aspartame, a source of phenylalanine. May be harmful for people with phenylketonuria

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 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 drugs should not be used together if doses of moclobemide higher than 150 mg twice a day 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 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 (e.g. 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 $5HT_{1B/1D}$ receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

4.6 Pregnancy and lactation

Pregnancy: The safety of this medical product for use in human pregnancy has not been established. Evaluation of experimental animal 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, and 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 (≥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), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Cardiac disorders:
Common: palpitations.
Uncommon: tachycardia; slight increase in blood pressure. Transient increases in systemic blood pressure.
Very rare: myocardial infarction; angina pectoris, coronary vasospasm.

Nervous system disorders:
Common: abnormalities or disturbances of sensation; dizziness; headache; hyperaesthesia; paraesthesia; somnolence; warm sensation.

Gastrointestinal disorders:
Common: abdominal pain, nausea, vomiting; dry mouth.
Very rare: ischemia or infarction (e.g. intestinal ischemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain.

Renal and urinary disorders:
Uncommon: polyuria; increased urinary frequency.
Very rare: urinary urgency.

Musculoskeletal and connective tissue disorders:
Common: muscle weakness; myalgia.

General disorders and administration site conditions:
Common: asthenia; heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

Immune system disorders:
Rare: hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions.

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 section 5.2) and therefore monitoring of patients after overdose with Zolmiles orodispersible 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 (5HT1) agonists. ATC code: N02CC03

Zolmitriptan has been demonstrated to be a selective agonist for $5HT_{1B/1D}$ receptors mediating vascular contraction. Zolmitriptan has high affinity for human recombinant $5HT_{IB}$ and $5HT_{ID}$ receptors, and modest affinity for $5HT_{IA}$ receptors. Zolmitriptan has no significant affinity or pharmacological activity at other 5HT receptor subtypes ($5HT_2$, $5HT_3$, $5HT_4$) 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 with zolmitriptan 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 Zolmiles 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 zolmitriptan 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 of zolmitriptan is rapid. In healthy volunteers, 75% of C_{max} 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 orodispersible tablet was demonstrated to be bioequivalent with the conventional tablet in terms of AUC and C_{max} for zolmitriptan and its active metabolite 183C91. Clinical pharmacology data show that the t_{max} for zolmitriptan can be later for the orally dispersible tablet (range 0.6 to 5h, median 3h) compared to the conventional tablet (range 0.5 to 3h, median 1.5h). The t_{max} for the active metabolite was similar for both formulations (median 3h).

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 zolmitriptan. 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 intravenous 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.
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

Mannitol (E421)
Calcium silicate
Microcrystalline cellulose
Aspartame (E951)
Sodium starch glycolate Type A
Crospovidone
Colloidal anhydrous silica
Magnesium stearate
Orange Cream Flavour (containing maltodextrin (maize), acacia (E414), ascorbic acid (E300), butylhydroxyanisole (E320))

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Peelable aluminium/aluminium blisters.

Pack sizes:
2, 3, 6 or 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/35/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 2009

10 DATE OF REVISION OF THE TEXT