Public Assessment Report

Decentralised Procedure

Zolmitriptan 2.5 mg film-coated tablets

PL 31609/0002

UK/H/1744/01/DC

Mepha Investigação, Desenvolvimento e Fabricação Famacêutica, Lda.
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Mepha Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. a Marketing Authorisation (licence) for the medicinal product Zolmitriptan 2.5 mg film-coated tablets (product licence number: PL 31609/0002) on 14 January 2011. This medicine is available on prescription only.

Zolmitriptan belongs to a group of medicines called the 5HT$_1$ agonists. Zolmitriptan 2.5 mg film-coated tablets are used to treat migraine attacks.

The data submitted in support of this application for Zolmitriptan 2.5 mg film-coated tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

### Information about Decentralised Procedure

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<td>Film-coated tablets, 2.5 mg</td>
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<td>Poland, Portugal</td>
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<td>9 September 2010</td>
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<tr>
<td>Marketing Authorisation number</td>
<td>PL 31609/0002</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Mepha Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. Lagoas Park, Edifício 5 A, Piso 2 2740-298 Porto Salvo Portugal</td>
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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Zolmitriptan 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 2.5 mg zolmitriptan.

Excipient:
Each film-coated tablet contains 100 mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Yellow, round, biconvex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Zolmitriptan is indicated for the acute treatment of migraine with or without aura.

4.2 Posology and method of administration
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.

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. Caution is advised due to an increased incidence of side effects. A controlled clinical study failed to demonstrate superiority of the 5 mg dose over the 2.5 mg dose. Nevertheless a 5 mg dose may be of benefit in some patients.

Zolmitriptan should not be dosed more than twice in 24 hours and the maximum daily dose should not exceed 10 mg.

Zolmitriptan 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 zolmitriptan in children is therefore not recommended.

Adolescents (12-17 years of age)
The efficacy of zolmitriptan 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
Safety and efficacy of zolmitriptan in individuals aged over 65 years have not been established. Use of zolmitriptan in the elderly is therefore not recommended.

Patients with 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.

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).

Interactions requiring dose adjustment (see section 4.5 Interactions)
A maximum dose of 5 mg in 24 hours is recommended for patients taking
- MAO-A inhibitors
- cimetidine
- specific inhibitors of CYP 1A2 such as fluvoxamine and the quinolones (eg ciprofloxacin)

Oral use.

4.3 Contraindications
- Known hypersensitivity to the active substance or to any of the excipients of the product.
- Moderate or severe hypertension, and mild uncontrolled hypertension.
- Ischaemic heart disease.
- Peripheral vascular disease
- Coronary vasospasm/Prinzmetal's angina.
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Concomitant administration of zolmitriptan with ergotamine, derivatives of ergotamine (including methysergide) or other 5-HT1 receptor agonists.
- Symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.
- 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. Care should be taken to exclude other potentially serious neurological conditions. There are no data on the use of zolmitriptan in hemiplegic or basilar 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 5HT1B/1D agonists.

In very rare cases, as with other 5HT1B/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 zolmitriptan, 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 5HT1B/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 5HT1B/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 5HT1B/1D agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

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 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
zolmitriptan and an SSRI or SNRI is clinically warranted, particularly during treatment initiation and dosage increases (see section 4.5).

As with other 5HT1B/1D 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.

Zolmitriptan film-coated tablets 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

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of zolmitriptan (for example beta blockers, oral dihydroergotamine, pizotifen).

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. Concomitant administration of other 5HT1B/1D agonists within 12 hours of zolmitriptan treatment should be avoided.

Data from healthy subjects suggest there are no pharmacokinetic or clinically significant interactions between zolmitriptan 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 zolmitriptan. Conversely it is advised to wait at least six hours following use of zolmitriptan before administering any ergotamine preparation (see section 4.3).

Following administration of 150 mg b. i. d 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.

As with other 5HT1B/1D receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

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 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).

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 fetus.

Lactation
Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human 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

There was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan. Use is unlikely to result in an impairment of the ability of patients to drive or operate machinery. However it should be taken into account that somnolence may occur.

4.8 Undesirable effects

The assessment of undesirable effects is based on the following frequency data:

- Very common: $\geq \frac{1}{10}$
- Common: $\geq \frac{1}{100}, < \frac{1}{10}$
- Uncommon: $\geq \frac{1}{1000}, < \frac{1}{100}$
- Rare: $\geq \frac{1}{10000}, < \frac{1}{1000}$
- Very rare: $< \frac{1}{10000}$
- Not known: cannot be estimated from the available data

Zolmitriptan 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.

Immune system disorders
Rare: anaphylaxis/anaphylactoid reactions, hypersensitivity reactions.

Nervous System disorders
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.

4.9 Overdose
Volunteers receiving single oral doses of 50 mg commonly experienced sedation.
The elimination half-life of zolmitriptan is 2.5 to 3 hours (see section 5.2) and therefore monitoring of patients after overdose with zolmitriptan 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
In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant 5HT1B and 5HT1D receptor subtypes. Zolmitriptan is a high affinity 5HT1B/1D receptor agonist with modest affinity for 5HT1A receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5HT2-, 5HT3-, 5HT4-, alpha1-, alpha2-, or beta1-, adrenergic; H1-, H2-, histaminic; muscarinic; dopaminergic1, or dopaminergic2 receptors. The 5HT1D 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.

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, administrated as tablets, shows comparable effect in migraine with or without aura and in menstrually associated migraine. Zolmitriptan tablets, if taken during aura, has not been demonstrated to prevent the migraine headache and therefore zolmitriptan 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

Absorption
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 (183C91, the N-desmethyl metabolite) which is also a 5HT1B/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 183C91, display dose-proportional AUC and C<sub>max</sub> over the dose range 2.5 to 50 mg. Absorption is rapid with 75% of C<sub>max</sub> 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.

Metabolism
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 (183C91) is active whilst the others are not. Plasma concentrations of 183C91 are approximately half those of the parent drug, hence it would therefore be expected to contribute to the therapeutic action of zolmitriptan.

Elimination
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\text{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\text{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 (t\text{½}) 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 t\text{½} 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 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.

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.

In a small group of healthy individuals there was no pharmacokinetic interaction with ergotamine. Concomitant administration of zolmitriptan with ergotamine/caffeine was well tolerated and did not result in any increase in adverse events or blood pressure changes as compared with zolmitriptan alone. 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.

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 5HT1B/1D receptor agonists, zolmitriptan binds to melanin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

*tablet core:*
lactose anhydrous
microcrystalline cellulose
sodium starch glycolate (Type A)
magnesium stearate (vegetal)

*film-coating:*
polyvinyl alcohol (partially hydrolyzed)
titanium dioxide (E171)
macrogol 3350
talc
iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

27 months

6.4 Special precautions for storage

Do not store above 30 °C
Store in the original package (blisters) in order to protect from moisture.

6.5 Nature and contents of container

OPA-Al-PVC/Al blisters
2, 3, 6, 10, 12, 18 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.
MARKETING AUTHORITY
Mepha Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda.
Lagoas Park, Edifício 5 A, Piso 2
2740-298 Porto Salvo
Portugal

MARKETING AUTHORITY NUMBER(S)
PL 31609/0002

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
14/01/2011

DATE OF REVISION OF THE TEXT
14/01/2011
Module 3

Product Information Leaflet

The following text is the approved Product Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Zolmitriptan 2.5 mg film-coated tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet
1. What Zolmitriptan 2.5 mg film-coated tablets are and what they are used for
2. Before you take Zolmitriptan 2.5 mg film-coated tablets
3. How to take Zolmitriptan 2.5 mg film-coated tablets
4. Possible side effects
5. How to store Zolmitriptan 2.5 mg film-coated tablets
6. Further information

1. WHAT ZOLMITRIPTAN 2.5 MG FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Zolmitriptan 2.5 mg belongs to a group of medicines called 5HT1 agonists.

Zolmitriptan 2.5 mg is used to treat migraine attacks.

2. BEFORE YOU TAKE ZOLMITRIPTAN 2.5 MG FILM-COATED TABLETS

Do not take this medicine if
- you are allergic (hypersensitive) to zolmitriptan or any of the other ingredients of Zolmitriptan 2.5 mg film-coated tablets (see section 6. Further information).
- you suffer from high blood pressure which is difficult to treat or have poorly controlled blood pressure. Speak to your doctor if unsure.
- you have poor blood flow in the arteries of the heart (ischaemic or coronary heart disease) or have other circulatory problems or suffer from a particular type of chest pain known as Prinzmetal’s angina.
- you suffer from a condition called Wolff-Parkinson-White Syndrome which is characterised by an abnormal heart rhythm
- you have had a stroke or symptoms similar to a stroke which wear off after a day or two (transient ischaemic attack).
- you are taking any medicines for migraine, including others of this type (5HT1 agonists) and ergotamine or ergot-type products. Zolmitriptan 2.5 mg should not be taken at the same time as these medicines (see section “Taking other medicines”).
- you suffer from kidney failure

Take special care with this medicine

Your doctor will decide if your headache is caused by migraine. You should take this medicine only for a migraine attack, not for other types of headache.

Before taking your tablets, tell your doctor if:
- You have ever had problems with your heart, including angina, heart attack or high blood pressure.
- You have ever been told that you may have an increased risk of heart disease.
- You have ever had any problems with your liver. Your dose may have to be reduced.
• Your migraine attack comes along with dizziness, double vision, impaired consciousness, slurred speech, incoordination, palsy (basilar migraine) or paralysis on one side of the body (hemiplegic migraine).
• You are taking a herbal remedy called St. John's wort.

If you take this medicine too often this may result in you getting a chronic headache. In such cases you should contact your doctor as you may have to stop taking this medicine.

If you get chest pain, stop taking this medicine until you have discussed the pain with your doctor.

Children and elderly patients
Zolmitriptan 2.5 mg is not recommended for people aged under 18 years or over 65.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

This particularly applies if you are also taking any of the following medicines during treatment with Zolmitriptan 2.5 mg:
• any other medicine for your migraine such as other 5HT1 agonists.
• medicines containing ergotamine or ergot-type medicines (like dihydroergotamine or methysergide). Do **not** take Zolmitriptan 2.5 mg within 24 hours after taking these drugs and do not take ergotamine or ergot-type medicines within 5 hours after taking Zolmitriptan 2.5 mg.
• any medicine for the treatment of depression; including medicines called monoamine oxidase inhibitors (MAOIs) like moclobemide, serotonin reuptake inhibitors (SSRIs) like fluoxetine, paroxetine, fluvoxamine or sertraline, or serotonin noradrenaline reuptake inhibitors (SNRIs) like venlafaxine or duloxetine.
• cimetidine (for stomach ulcers) or a quinolone antibiotic such as ciprofloxacin (ask your doctor if you are not sure).
• the herbal remedy St. John’s wort. If you already take a St. John’s wort preparation, stop taking it and mention this to your doctor at your next visit.

Pregnancy and breast-feeding

Ask your doctor for advice if you are pregnant, trying to get pregnant, or breast-feeding.
It is not known whether this medicine is harmful to an unborn baby when taken by a pregnant woman.

Breast-feeding should be avoided for 24 hours after taking this medicine.

Driving and using machines

This medicine is unlikely to affect your ability to drive or use machinery. But you should wait to see how it affects you before you try these activities.

Important information about some of the ingredients of Zolmitriptan 2.5 MG

Each film-coated tablet contains 100 mg lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ZOLMITRIPHTAN 2.5 MG FILM-COATED TABLETS

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet or two tablets (2.5 mg or 5 mg Zolmitriptan) as soon as you feel your migraine start.
If you take a higher dose (5 mg) you are more likely to suffer side effects.
If your migraine has not gone after two hours, or it comes back within 24 hours, take another tablet. Do not take Zolmitriptan 2.5 mg more than 2 times within 24 hours.

If these tablets do not work, tell your doctor. Your doctor may want to change your treatment.

If you take more Zolmitriptan 2.5 mg than you should

If you take more tablets than your doctor told you to take, contact your doctor or nearest hospital. Remember to take your tablets with you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zolmitriptan 2.5 mg can cause side effects, although not everybody gets them.

If you experience any of the following side effects, stop taking your medicine and seek immediate medical advice:
- Hypersensitivity reactions including itchy rash, swelling of the mouth, tongue and neck, with fluid in the tissues (angioœdemata) and anaphylaxis or anaphylactoid reactions (serious allergic-type reactions).
- Pains in the chest (Angina), spasm of the blood vessels of the heart, heart attack.
- Bloody diarrhoea or other serious complication with gut and stomach.

Side effects are usually mild to moderate.

Common (affects 1 to 10 users in 100):
- Feeling or being sick. Feeling dizzy, sleepy, warm or weak.
- Dry mouth.
- Stomach pain.
- Headache (overuse of this type of medicine may cause an increased number of headaches, tell your doctor if this happens).
- An uneven heart beat.
- Feelings of heaviness, tightness, pain or pressure in your throat, neck, chest, arms or legs.
- Aches and pains in your muscles, or muscle weakness.
- Tingling in your fingers and toes, a loss of sense of touch, or skin that is sensitive to touch.

Uncommon (affects 1 to 10 users in 1,000):
- Very fast heart beat, slightly higher blood pressure
- Increase in the amount of water (urine) you pass, or in how often you need to pass water.

Very rare (affects less than 1 user in 10,000):
- Urge to urinate

People who get migraines may be at risk of certain problems of the blood circulation in the brain, such as cerebral bleeding (bleeding in the brain) or strokes. As with other drugs of this type, these problems have been reported in very rare cases.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZOLMITRIPTAN 2.5 MG FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month.
Do not store above 30 °C.
Store in the original package (blisters) in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Zolmitriptan 2.5 mg contains

The active substance is zolmitriptan.

Each film-coated tablet contains 2.5 mg zolmitriptan.

The other ingredients are

tablet core:
lactose anhydrous
microcrystalline cellulose
sodium starch glycolate (Type A)
magnesium stearate (vegetal)

film-coating:
polyvinyl alcohol (partially hydrolyzed)
titanium dioxide (E171)
macrogl 3350
talc
iron oxide yellow (E172)

What Zolmitriptan 2.5 mg looks like and contents of the pack

Yellow, round, biconvex tablet.

Zolmitriptan 2.5 mg is available in blister packs containing 2, 3, 6, 10, 12 and 18 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Mepha Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. Lagoas Park, Edificio 5 A, Piso 2 2740-298 Porto Salvo, Portugal

Manufacturer:
Merckle GmbH, Ludwig-Merckle-Strasse 3, D-89143 Blaubeuren, Germany

This leaflet was last revised in January 2011

PL 31609/0002
Module 4

Labelling

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

carton

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 2.5 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg zolmitriptan.

3. LIST OF EXCIPIENTS

Contains lactose.
Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

2 film-coated tablets
3 film-coated tablets
6 film-coated tablets
10 film-coated tablets
12 film-coated tablets
18 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

oral use
Please read the enclosed package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.
Store in the original package (blisters) in order to protect from moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mepha Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. Lagoas Park, Edificio 5 A, Piso 2 2740-298 Porto Salvo, Portugal

12. MARKETING AUTHORISATION NUMBER(S)

PL 31609/0002

13. BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Zolmitriptan 2.5 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

[NATURE/TYPE]

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 2.5 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mepha Investigação

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
Module 5

Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Zolmitriptan 2.5 mg film-coated tablets in the acute treatment of migraine headache, with or without aura, could be approved.

EXECUTIVE SUMMARY

Problem statement
This Decentralised application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that the proposed product is a generic version of the product Zomig 2.5 mg film-coated tablets (AstraZeneca), which was first licensed in Sweden in 1997. The reference product has, therefore, been authorised in the EEA for at least 10 years and the legal basis of this application is acceptable.

With the UK as the Reference Member State in this Decentralised Procedure (DCP), Mepha Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. is applying for a Marketing Authorisation for Zolmitriptan 2.5 mg film-coated tablets in Poland and Portugal.

About the product
Zolmitriptan is a selective agonist for 5HT1B/1D receptors and when zolmitriptan binds to these receptors the cranial blood vessels constrict. Zolmitriptan has high affinity for human recombinant 5HT1B and 5HT1D receptors, and modest affinity for 5HT1A receptors. Zolmitriptan has no significant affinity for or pharmacological activity at other 5HT receptor subtypes (5HT2, 5HT3, 5HT4) or adrenergic, histaminic, muscarinic or dopaminergic receptors.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

**GLP**
No new preclinical studies were submitted in support of this application, and none are needed for an application of this type.

**GCP**
Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**

- **rINN:** Zolmitriptan
- **Chemical names:**
  - (4S)-4-[[3-[2-(dimethyl amino) ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone
  - N, N-dimethyl-2-[5-(2-oxo-1, 3oxazolidin-4-yl-methyl)-1H-indol-3-yl]-ethyl amine

**Structural formula:**

* Asymmetric carbon

**Molecular Formula:** C_{16}H_{21}N_{3}O_{2}
**Molecular weight:** 287.36
**Physical characteristics:** Off-white to cream coloured crystalline powder.
**Solubility:** Freely soluble in methanol. The aqueous solubility is slightly soluble at pHs 2-3 but very slightly soluble at pHs 4-7.

There are no Ph. Eur. or BP monographs for zolmitriptan. The quality of the substance is suitably controlled by in-house specifications.
Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**Drug product**
The tablet’s core contains lactose anhydrous, microcrystalline cellulose, sodium starch glycolate (Type A) and magnesium stearate (vegetal). The tablet’s film-coating is Opadry II Yellow 85F92473, which comprises polyvinyl alcohol (partially hydrolyzed), titanium dioxide (E171), macrogol 3350, tale and iron oxide yellow (E172).

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of Opadry II Yellow 85F92473, which is controlled to in-house specifications. In the absence of a European Pharmacopoeia monograph for this excipient, this is acceptable. Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

**Pharmaceutical development**
The objective of the development programme was to develop a formulation similar to the innovator product, Zomig 2.5 mg film-coated tablets, manufactured by AstraZeneca. A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.
Manufacturing process
A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. Although batch results on pilot scale batches show batch to batch consistency and suggest that the critical process parameters have been identified, in view of the minimal process validation/in-process data submitted, batch sizes are restricted to batch sizes for which satisfactory batch results have been submitted with a commitment to fully validate the approved batch sizes prior to marketing.

Finished product specification
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-closure system
The finished product is stored in OPA-Al-PVC/Al blister packs. Pack sizes are 2, 3, 6, 10, 12, or 18 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

Stability of the product
Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 27 months for this product when the storage precautions ‘Do not store above 30 °C’ and ‘Store in the original package (blisters) in order to protect from moisture’ are applied.

Product literature
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Quality conclusion
There are no objections to the approval of Zolmitriptan 2.5 mg film-coated tablets from a quality point of view.
Preclinical aspects

Preclinical overview
The pharmacological, pharmacokinetic and toxicological properties of zolmitriptan are well known. As zolmitriptan is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

Expert report
The preclinical overview has been written by a medical doctor. The overview, dated 27 October 2008, refers to 26 references from the published literature dated up to 2008. In view of the fact that the pharmaco-toxicological properties of zolmitriptan are well known, the overview is acceptable.

Environmental risk assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all zolmitriptan-containing products, which in turn is unlikely to increase exposure of the environment to zolmitriptan.

Product literature
The product literature is acceptable from a preclinical point of view.

Preclinical conclusion
There are no objections to the approval of Zolmitriptan 2.5 mg film-coated tablets from a preclinical point of view.

Clinical aspects

Pharmacokinetics
To support the application, the applicant has conducted a bioequivalence study comparing Zolmitriptan 5 mg film-coated tablets with Zomig 5 mg film-coated tablets. The study was performed using a higher strength (5 mg) version of the proposed product as the DCP for Zolmitriptan 2.5 mg film-coated tablets ran in parallel with another DCP for the higher strength product and these Decentralised applications were supported by the same data. The company’s clinical expert has provided the following justification for studying the 5 mg strength only, rather than both strengths:

a. The pharmacokinetics of zolmitriptan are linear
b. The qualitative composition of the two tablet strengths is the same
c. The ratio between active substance and the excipients are the same across the different strengths
d. The dissolution rate of the highest strength of the test product in-vitro is similar to that of the lower strengths, and the dissolution rate of both strengths of the test
product in vitro are similar to the dissolution rates of the corresponding strengths of the reference product

Satisfactory justification is provided for a bio-waiver for Zolmitriptan 2.5 mg film-coated tablets. As Zolmitriptan 2.5 mg and 5 mg film-coated tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 5 mg strength tablets can be extrapolated to the 2.5 mg strength tablets.

Study method
This single dose, randomized, two-way crossover study was performed under fasting conditions in 48 health male subjects.

A single oral dose was administered in each study period. Each period was separated by a wash-out of 7 days. Blood samples were collected prior to up to 24 hours after drug administration.

Statistical analysis based on a parametric ANOVA model of the pharmacokinetic parameters; two-sided 90% confidence interval of the ratio of geometric means for the $C_{\text{max}}$, $AUC_T$ and $AUC_{\infty}$ based on ln-transformed data; $T_{\text{max}}$ non-parametric.

Results

\[
\begin{array}{|c|cc|cc|}
\hline
\text{PARAMETER} & \text{TEST} & \text{REFERENCE} \\
 & \text{MEAN} & \text{C.V.} (%) & \text{MEAN} & \text{C.V.} (%) \\
\hline
C_{\text{max}} (\text{pg/mL}) & 9185.6 & 31.4 & 8748.7 & 27.6 \\
\ln (C_{\text{max}}) & 9.0781 & 3.4 & 9.0391 & 3.1 \\
T_{\text{max}} (\text{hours}) * & 1.25 & 71.8 & 1.25 & 69.9 \\
AUC_T (\text{pg.h/mL}) & 52563.8 & 30.7 & 53210.6 & 31.1 \\
\ln (AUC_T) & 10.8245 & 2.9 & 10.8359 & 2.9 \\
AUC_{\infty} (\text{pg.h/mL}) & 54274.3 & 31.0 & 54731.5 & 31.3 \\
\ln (AUC_{\infty}) & 10.8562 & 2.8 & 10.8637 & 2.9 \\
AUC_{T/\infty} (%) & 96.90 & 2.3 & 97.27 & 1.6 \\
K_{\text{ef}} (\text{hours}^{-1}) & 0.1377 & 27.4 & 0.1433 & 22.2 \\
T_{\text{ef}} (\text{hours}) & 5.44 & 29.4 & 5.10 & 24.4 \\
\hline
\end{array}
\]

*median is present

\[
\begin{array}{|c|ccc|ccc|}
\hline
\text{PARAMETER} & \text{INTRA-SUBJECT} & \text{GEOMETRIC LSMEANS *} & \text{RATIO} & \text{90% CONFIDENCE} \\
 & \text{CV} (%) & \text{TEST} & \text{REFERENCE} & \text{(%)} & \text{LIMITS (%)} \\
 & & & & & \text{LOWER} & \text{UPPER} \\
\hline
C_{\text{max}} & 19.9 & 8761.5 & 8426.4 & 103.98 & 97.19 & 111.23 \\
AUC_T & 11.3 & 50235.9 & 50811.9 & 98.87 & 95.12 & 102.76 \\
AUC_{\infty} & 11.1 & 51855.8 & 52245.6 & 99.25 & 95.55 & 103.10 \\
\hline
\end{array}
\]
*units are pg/mL for C\text{max} and pg.h/mL for AUC\text{T} and AUC\text{∞}*

These results are within conventional bioequivalence criteria, with the 90% confidence intervals between 80-125%.

**Conclusion**

Based on the submitted bioequivalence study Zolmitriptan 5 mg film-coated tablets are considered bioequivalent to Zomig 5 mg film-coated tablets.

As Zolmitriptan 2.5 mg and 5 mg film-coated tablets, hard meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 5 mg strength tablets can be extrapolated to the 2.5 mg strength tablets.

**Pharmacodynamics**

The pharmacodynamic characteristics of zolmitriptan have been well-studied in the past. There would be no particular concerns for a generic medicinal product. No new data have been submitted and none are required.

**Clinical efficacy and safety**

No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of zolmitriptan.

**Pharmacovigilance system**

The RMS considers that the pharmacovigilance system fulfils the requirements. The Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

**Risk management plan**

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

**Expert report**

A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.

**Product literature**

All product literature (SmPC, PIL and labelling) is medically satisfactory.

**Clinical conclusion**

There are no objections to the approval of Zolmitriptan 2.5 mg film-coated tablets from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Zolmitriptan 2.5 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of these type.

EFFICACY
The use of zolmitriptan in the treatment of migraine is well established. Bioequivalence has been demonstrated between the Zolmitriptan 5 mg film-coated tablets and its reference product and the results and conclusions of the bioequivalence study on the 5 mg strength tablets can be extrapolated to the 2.5 mg strength tablets. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with zolmitriptan is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is, therefore, considered to be positive. A Marketing Authorisation should be granted.