ZOLMITRIPTAN 2.5 MG ORODISPERSIBLE TABLETS
ZOLMITRIPTAN 5 MG ORODISPERSIBLE TABLETS

(Zolmitriptan)

PL 24668/0137-8

UKPAR

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LAY SUMMARY

The MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Zolmitriptan 2.5 mg and 5 mg orodispersible tablets on 21 September 2011. These products are prescription-only medicines (POM) used to treat migraine headache.

Migraine symptoms may be caused by the widening of blood vessels in the head. Zolmitriptan is thought to reduce the widening of these blood vessels. This helps to take away the headache and other symptoms of a migraine attack, such as feeling or being sick (nausea or vomiting) and being sensitive to light and sound.

Zolmitriptan belongs to a group of medicines called triptans.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Zolmitriptan 2.5 mg and 5 mg orodispersible tablets outweigh the risks, hence Marketing Authorisations has been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Caduceus Pharma Limited, Marketing Authorisations for the medicinal products Zolmitriptan 2.5 mg and 5 mg orodispersible tablets (PL 24668/0137-8) on 21 September 2011. These products are prescription-only medicines (POM) indicated for acute treatment of migraine headache with or without aura.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Zomig tableetter 2.5 mg and 5 mg Film-coated tablets (AstraZeneca AB, Sweden), which have been authorised in the EEA since 21 March 1997. The corresponding reference products in the UK are Zomig Rapimelt 2.5mg and 5mg orodispersible tablets (AstraZeneca UK Limited), which were first authorised on 20 June 2001 and 21 September 2004 respectively. The product used in the bioequivalence study was AscoTop 5mg orodispersible tablets (AstraZeneca GmbH), taken from the German market. It has been confirmed that this can be considered equivalent to the same product from the UK market.

Zolmitriptan has been demonstrated to be a selective agonist for 5HT1B/1D receptors mediating vascular contraction. Zolmitriptan has high affinity for human recombinant 5HT1B and 5HT1D receptors, and modest affinity for 5HT1A receptors. Zolmitriptan has no significant affinity or pharmacological activity at other 5HT receptor subtypes (5HT2, 5HT3, 5HT4) or adrenergic, histaminic, muscarinic or dopaminergic receptors.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

One single-dose, bioequivalence study under fasting conditions was submitted to support these applications, comparing the test product Zolmitriptan 5 mg orodispersible tablets (Caduceus Pharma Limited) and the reference product AscoTop 5mg orodispersible tablets (AstraZeneca GmbH, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being a generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns were raised during the assessment of these applications and it was, therefore, judged that the benefits of taking Zolmitriptan 2.5 mg and 5 mg orodispersible tablets outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Zolmitriptan
Chemical name: (4S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]Methyl]-1,3-oxazolidin-2-one

(S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidinyl methyl)-1H-indol-3-yl]ethylamine

Structure:

[Image of chemical structure]

Molecular formula: C_{16}H_{21}N_{3}O_{2}
Molecular weight: 287.36
Appearance: Zolmitriptan is a white to cream coloured powder which is freely soluble in methanol.

Zolmitriptan is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials 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 active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the 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 to support a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, mannitol (E421), calcium silicate, microcrystalline cellulose, aspartame (E951), sodium starch glycolate Type A, crospovidone, colloidal anhydrous silica, magnesium stearate and Orange Cream Flavour
(containing e.g. maltodextrin [maize], acacia [E414], ascorbic acid [E300],
butylhydroxyanisole [E320])

Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph with
the exception of calcium silicate which is compliant with National Formulary-US
pharmacopoeia (USP) and Orange Cream Flavour, which is controlled to suitable in-house
specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically
modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical development
The aim of the development programme was to formulate safe, efficacious, tablets with a
fast disintegration that could be considered generic medicinal products of AscoTop 2.5 mg
and 5mg orodispersible tablets (AstraZeneca GmbH, Germany).

Suitable pharmaceutical development data have been provided for these applications.

Comparable in vitro dissolution and impurity profiles have been provided for the proposed
and originator product.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of all strengths of the
product, along with an appropriate account of the manufacturing process. The
manufacturing process has been validated at pilot scale and has shown satisfactory results.
In addition, commitments have been provided for validation of production scale batches.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and
have been adequately validated, as appropriate. Batch data have been provided and comply
with the release specification. Certificates of Analysis have been provided for any working
standards used.

Container Closure System
All strengths of the finished product are packaged in aluminium/aluminium blister strips
and are available in pack sizes of 2, 3, 6 and 12 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing
authorisation holder has committed to submitting the mock-ups for any pack size to the
relevant regulatory authorities for approval before marketing.

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 food.
Stability
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no special storage conditions.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PILs and labelling are satisfactory.

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.

MAA Form
The MAA forms are satisfactory.

Expert Report
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that marketing authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed products are generic medicinal products of originator products that have been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
It is recommended that marketing authorisations are granted for these applications.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of zolmitriptan is well-known. With the exception of the bioequivalence study, no pharmacokinetic or pharmacodynamic data were submitted for these applications, and none were required for applications of this type.

The following bioequivalence study was submitted:

An open label, randomised, single dose, two-way crossover study to compare the pharmacokinetics of the test product Zolmitriptan 5 mg orodispersible tablets versus the reference product AscoTop 5mg orodispersible tablets (AstraZeneca GmbH, Germany) in healthy adult volunteers under fasted conditions.

All volunteers were dosed in a fasted state in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for zolmitriptan, for the test product versus the reference product are presented below as geometric mean values with ratios of least-square means.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/ml)</th>
<th>AUC_{0-∞} (ng.h/ml)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>63196.09</td>
<td>65118.46</td>
<td>10315.03</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>65053.33</td>
<td>67058.15</td>
<td>11393.68</td>
</tr>
<tr>
<td>Ratio T/R (90% CI*)</td>
<td>95.23%</td>
<td>95.19%</td>
<td>90.39%</td>
</tr>
<tr>
<td></td>
<td>(90.64-100.06%)</td>
<td>(90.79-99.80%)</td>
<td>(84.25-96.98%)</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours  
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity  
C_{max} maximum plasma concentration  
90% CI* 90% Geometric Confidence Interval using log-transformed data

The 90% confidence intervals for AUC and C_{max} for test versus reference product for zolmitriptan are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1).

Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 2.5 mg strength of the product meets the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to the 2.5 mg strength.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.
Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are acceptable. The SmPC for each strength is consistent with that for it's respective originator product. The PIL is consistent with the SmPC and in-line current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Zolmitriptan 2.5 mg and 5 mg orodispersible 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Zolmitriptan 2.5 mg and 5 mg orodispersible tablets and its respective reference product (AscoTop 2.5 mg and 5mg orodispersible tablets). As the 2.5 mg strength of the product meets the biowaiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to the 2.5 mg strength tablet.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of zolmitriptan is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with zolmitriptan is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
ZOLMITRIPTAN 2.5 MG ORODISPERSIBLE TABLETS
ZOLMITRIPTAN 5 MG ORODISPERSIBLE TABLETS

PL 24668/0137-8

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation applications on 12 March 2008.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 19 March 2008.

3. Following assessment of the applications the MHRA requested further information relating to the quality dossier on 23 September 2008 and 21 July 2011.

4. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 08 June 2009 and 11 August 2011.

5. The applications were determined on 21 September 2011.
ZOMITRIPTAN 2.5 MG ORODISPERSIBLE TABLETS
ZOMITRIPTAN 5 MG ORODISPERSIBLE TABLETS

PL 24668/0137-8

STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Zolmitriptan 2.5 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2.5 mg orodispersible tablet contains 2.5 mg zolmitriptan.

Excipient: aspartame (4 mg).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet.
White, round flat tablets with the diameter 7.5 mm.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Acute treatment of migraine headache with or without aura.

4.2 Posology and method of administration
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 tablets 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\textsubscript{1B/1D} receptor agonists), has been associated with coronary vasospasm, as a result, patients with ischaemic heart disease were excluded from clinical trials. Therefore zolmitriptan 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\textsubscript{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\textsubscript{1B/1D} agonists. It should be noted that migraineurs 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\textsubscript{1B/1D} agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. Zolmitriptan 2.5mg orodispersible tablets 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\textsubscript{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\textsubscript{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.

Zolmitriptan 2.5mg orodispersible tablets contain 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<sub>1B/1D</sub> 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 of up to 20 mg of 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 orders:**

*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 Zolmitriptan 2.5 mg 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_{1B} and 5HT_{1D} receptors, and modest affinity for 5HT_{1A} 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 Zolmitriptan 2.5mg orodispersible tablets 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.

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 e.g. 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
No special requirements

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

7 MARKETING AUTHORIZATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 24668/0137

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
21/09/2011

10 DATE OF REVISION OF THE TEXT
21/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Zolmitriptan 5 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 mg orodispersible tablet contains 5 mg zolmitriptan.

Excipient: aspartame (8mg).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet.
White, 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 zolmitriptan 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 migraineurs 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. Zolmitriptan 5mg orodispersible tablets 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.

Zolmitriptan 5mg orodispersible tablets contain 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<sub>1B/1D</sub> 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 of up to 20 mg of 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 orders:
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 Zolmitriptan 2.5 mg 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 5HT1B/1D Receptors mediating vascular contraction. Zolmitriptan has high affinity for human recombinant 5HT1B and 5HT1D receptors, and modest affinity for 5HT1A receptors. Zolmitriptan has no significant affinity or pharmacological activity at other 5HT receptor subtypes (5HT2, 5HT3, 5HT4) 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 Zolmitriptan 5mg orodispersible tablets 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 5HT1B/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 Cmax over the dose range 2.5 to 50 mg. Absorption of zolmitriptan is rapid. In healthy volunteers, 75% of Cmax 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 Cmax for zolmitriptan and its active metabolite 183C91. Clinical pharmacology
data show that the \( t_{\text{max}} \) 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 \( t_{\text{max}} \) 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 \( C_{\text{max}} \) 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\textsubscript{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 e.g. 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
No special requirements

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

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0138

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/09/2011

10 DATE OF REVISION OF THE TEXT
21/09/2011
Module 3

PATIENT INFORMATION LEAFLET

The following text is the approved Patient 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 and 5 mg orodispersible tablets

Zolmitriptan

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 is and what it is used for
2. Before you take Zolmitriptan
3. How to take Zolmitriptan
4. Possible side effects
5. How to store Zolmitriptan
6. Further information

1. WHAT ZOLMITRIPTAN IS AND WHAT IT IS USED FOR

Zolmitriptan orodispersible tablets contain zolmitriptan and belong to a group of medicines called triptans.

Zolmitriptan is used to treat migraine headache.

Migraine symptoms may be caused by the widening of blood vessels in the head. Zolmitriptan is thought to reduce the widening of these blood vessels. This helps to take away the headache and other symptoms of a migraine attack, such as feeling or being sick (nausea or vomiting) and being sensitive to light and sound.

Zolmitriptan works only when a migraine attack has started. It will not stop you from getting an attack.

2. BEFORE YOU TAKE ZOLMITRIPTAN

Do not take Zolmitriptan
- if you are allergic (hypersensitive) to zolmitriptan or any of the other ingredients of this medicine (see section 6: Further Information)
- if you have high blood pressure
- if you have ever had heart problems, including a heart attack, angina (chest pain caused by exercise or effort), Prinzmetal’s angina (chest pain which happens at rest) or have experienced heart related symptoms such as shortness of breath or pressure over the chest
- if you have had a stroke or short-lasting symptoms similar to stroke (transient ischaemic attack or TIA)
- if you have severe kidney problems
- if you are at the same time taking some other medicines for migraine (e.g. ergotamine or ergot-type medicines like dihydroergotamine and methysergide) or other triptan medicines for migraine. See section below: ‘Taking other medicines’ for further information.

If you are not sure if any of these apply to you, talk to your doctor or pharmacist.

**Take special care with Zolmitriptan**

Before you take Zolmitriptan, tell your doctor if:

- you are at risk of getting ischaemic heart disease (poor blood flow in the arteries of the heart). Your risk is greater if you smoke, have high blood pressure, high levels of cholesterol, diabetes or if anyone in your family has ischaemic heart disease
- you have been told that you have Wolff-Parkinson-White Syndrome (a type of abnormal heart beat)
- you have ever had liver problems
- you have headaches which are not like your usual migraine headache
- you are taking any other medicine for treatment of depression (see ‘Taking other medicines’ later in this section).

When Zolmitriptan is taken at the same time as medicines of the type SSRI or SNRI, which are used for the treatment of depression, there is a risk of development of so called serotonin syndrome. The symptoms can be severe and include shivering, over-reactive reflexes, nausea, fever, sweating, delirium, mental confusion and coma. In case you are taking this combination your doctor should monitor you carefully, especially in the beginning of treatment, when doses are increased or if another serotonergic medication is added. If you experience any of these symptoms contact a doctor as soon as possible.

If you go into hospital tell the medical staff you are taking Zolmitriptan.

Zolmitriptan is not recommended for people aged under 18 years or over 65.

As with other migraine treatments, using too much Zolmitriptan can cause daily headaches or can make your migraine headaches worse. Ask your doctor if you think that this is the case for you. You may need to stop using Zolmitriptan to correct the problem.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without prescription and herbal medicines. In particular, tell your doctor if you are taking any of the following medicines:

**Medicines for migraine**
- other triptans than zolmitriptan
- if you take medicines containing ergotamine or ergot-type medicines (such as dihydroergotamine or methysergide), leave 24 hours before taking Zolmitriptan.
- after taking Zolmitriptan leave 6 hours before taking ergotamine or ergot-type medicines.

**Medicines for depression (see also section Take special care with Zolmitriptan above)**
- moclobemide or fluvoxamine
- medicines called SSRIs (selective serotonin reuptake inhibitors)
- medicines called SNRIs (serotonin norepinephrine reuptake inhibitors) such as venlafaxine or duloxetine

**Other medicines**
- cimetidine (for indigestion or stomach ulcers)
- a quinolone antibiotic (such as ciprofloxacin)

If you are using herbal remedies containing St John’s Wort (*Hypericum perforatum*), side effects of Zolmitriptan may be more likely to happen.

**Taking Zolmitriptan orodispersible tablets with food and drink**
You can take Zolmitriptan with or without food. It does not affect the way that Zolmitriptan works.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

It is not known if taking Zolmitriptan during pregnancy is harmful. Before taking Zolmitriptan, tell your doctor if you are pregnant or trying to become pregnant.

Do not breast-feed within 24 hours of taking Zolmitriptan.

**Driving and using machines**
During a migraine attack your reactions may be slower than usual. Bear this in mind when you drive or use any tools or machines.

Zolmitriptan is unlikely to affect driving or using tools or machines. However, it is best to wait to see how Zolmitriptan affects you before you try these activities.
Important information about some of the ingredients of Zolmitriptan

Zolmitriptan orodispersible tablets contain source of phenylalanine. May be harmful for people with phenylketonuria.

3. HOW TO TAKE ZOLMITRIPTAN

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

You can take Zolmitriptan as soon as a migraine headache starts. You can also take it once an attack is underway.

The usual dose is one tablet (either 2.5 mg or 5 mg).

You can take another tablet if the migraine is still present after two hours or if it returns within 24 hours.

If the tablets did not give you enough help with your migraine, tell your doctor. Your doctor may raise the dose to 5 mg or change your treatment.

Do not use more than the dose prescribed for you.

Do not use more than two doses in one day. If you have been prescribed the 2.5 mg tablet, the maximum daily dose is 5 mg. If you have been prescribed the 5 mg tablet, the maximum daily dose is 10 mg.

*Instruction for use*

1. Peel the blister pack open. Do not push the tablet through the foil.
2. Place the tablet on your tongue, where it will dissolve and be swallowed with the saliva. You do not have to take a drink of water in order to swallow your tablet.

*If you take more Zolmitriptan than you should*

If you have taken more Zolmitriptan than prescribed by your doctor, tell your doctor or go to the nearest hospital straight away. Take the Zolmitriptan medicine with you.

When too many orodispersible tablets are taken the symptoms may possible include sedation.

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 can cause side effects, although not everybody gets them. Some of the symptoms below could be part of the migraine attack itself.
**Common side effects (affects 1 to 10 users in 100):**
- Abnormal sensations such as tingling in your fingers and toes or skin that is sensitive to touch.
- Feeling sleepy, dizzy or warm
- Headache
- Uneven heart beat
- Feeling sick, vomiting
- Stomach pain
- Dry mouth
- Muscle weakness or muscle pain
- Feeling weak
- Heaviness, tightness, pain or pressure in throat, neck, arms and legs, or chest

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

**Rare side effects (affects 1 to 10 users in 10,000):**
- Allergic/ hypersensitivity reactions including lumpy rash (hives) and swelling of the face, lips, mouth, tongue and throat. If you think that Zolmitriptan is causing an allergic reaction, stop using it and contact your doctor straight away.

**Very rare side effects (affects less than 1 user in 10,000):**
- Angina (pain in the chest, often brought on by exercise), heart attack or spasm of the blood vessels of the heart. If you notice chest pain or shortness of breath after taking Zolmitriptan, contact your doctor and do not take any more Zolmitriptan.
- Spasm of the blood vessels of the gut, which can cause damage to your gut. You may notice stomach pain or bloody diarrhoea. If this happens, contact your doctor and do not take any more Zolmitriptan.

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**

Keep out of the reach and sight of children.

Do not use Zolmitriptan after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.

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 contains**

- The active substance is zolmitriptan. Zolmitriptan orodispersible tablets contain either 2.5 mg or 5 mg of zolmitriptan.
- The other ingredients are mannitol (E421), calcium silicate, microcrystalline cellulose, aspartame (E951), sodium starch glycolate type A, crospovidone, colloidal anhydrous silica, magnesium stearate and orange cream flavour (containing e.g. maltodextrin (maize), acacia (E414), ascorbic acid (E300), butylhydroxyanisole (E320)).

**What Zolmitriptan looks like and contents of the pack**

Zolmitriptan 2.5 mg orodispersible tablets are white and round flat tablets with the diameter 7.5 mm.

Zolmitriptan 5 mg orodispersible tablets are white and round flat tablets with the diameter 9.5 mm.

Zolmitriptan orodispersible tablets 2.5 mg and 5 mg come in peelable aluminium laminate blister packs containing 2, 3, 6 or 12 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:
CADUCEUS PHARMA LIMITED
6th Floor
94 Wigmore street
London
W1U 3RF
UK

Manufacturer:

Actavis Limited
BLB016, Bulebel Industrial Estate
ZTN3000
Malta

*This leaflet was last updated in November 2010*
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 AND THE IMMEDIATE PACKAGING

Cartons

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 2.5 mg orodispersible tablets

Zolmitriptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 2.5 mg zolmitriptan.

3. LIST OF EXCIPIENTS

Contains aspartame.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 orodispersible tablets
3 orodispersible tablets
6 orodispersible tablets
12 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instruction for use
1. Peel the blister pack open. Do not push the tablet through the foil.
2. Place the tablet on your tongue, where it will dissolve and be swallowed with the saliva. You do not have to take a drink of water in order to swallow your tablet.

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

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

Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0137

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zolmitriptan 2.5 mg orodispersible tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 2.5 mg orodispersible tablets

Zolmitriptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma LTD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Cartons

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 5 mg orodispersible tablets

Zolmitriptan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 5 mg zolmitriptan.

3. LIST OF EXCIPIENTS

Contains aspartame.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 orodispersible tablets
3 orodispersible tablets
6 orodispersible tablets
12 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instruction for use
1. Peel the blister pack open. Do not push the tablet through the foil.
2. Place the tablet on your tongue, where it will dissolve and be swallowed with the saliva. You do not have to take a drink of water in order to swallow your tablet.

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

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

Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0138

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zolmitriptan 5 mg orodispersible tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan 5 mg orodispersible tablets

Zolmitriptan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma LTD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER