Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zolmitriptan Teva 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg zolmitriptan.

Excipients:
Each film-coated tablet contains 91.46 mg lactose.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, biconvex yellow film-coated tablets engraved with ‘Z2.5’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute treatment of migraine headache with or without aura.

4.2 Posology and method of administration

The recommended dose of Zolmitriptan Teva tablets to treat a migraine attack is 2.5 mg. It is advisable that Zolmitriptan Teva tablets are taken as early as possible after the onset of migraine headache but they are also effective if taken at a later stage.
The tablets should be swallowed whole and with water.
If symptoms of migraine should recur within 24 hours following an initial response, a second dose may be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose. If a patient does not respond to the first dose, it is unlikely that a second dose will be of benefit in the same attack.
If a patient does not achieve satisfactory relief with 2.5 mg doses, for subsequent attacks 5 mg doses of Zolmitriptan Teva 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.
The total daily intake should not exceed 10 mg. Not more than 2 doses of Zolmitriptan Teva should be taken in any 24 hour period.
Zolmitriptan Teva 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 Teva in children is therefore not recommended.

Adolescents (12 - 17 years of age)
The efficacy of Zolmitriptan Teva tablets was not demonstrated in a placebo controlled clinical trial for patients aged 12 to 17 years. Use of Zolmitriptan Teva tablets in adolescents is therefore not recommended.

Use in patients aged over 65 years
The safety and efficacy of zolmitriptan in individuals aged over 65 years have not been established. Use of Zolmitriptan Teva in the elderly is therefore not recommended.

Patients with hepatic impairment
Patients with mild or moderate hepatic impairment require no dose adjustment, however for patients with severe hepatic impairment, a maximum dose of 5 mg in 24 hours is recommended.

Patients with renal impairment
No dosage adjustment required in patients with a creatinine clearance of more than 15 ml/min. (See Section 4.3 Contraindications and Section 5.2 Pharmacokinetic Properties)

Interactions requiring dose adjustment (see Section 4.5 Interactions)
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 (eg ciprofloxacin).

4.3 Contraindications

Zolmitriptan Teva is contraindicated in patients with known hypersensitivity to zolmitriptan, sunset yellow (E110), allura red AC (E129) 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 Teva 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 no 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 ophthalmophlegic migraine. Stroke and other cerebrovascular events such as cerebral haemorrhagic accidents, subarachnoidal hemorrhages and cerebrovascular accidents have been reported in patients treated with $5HT_{1B/1D}$ agonists, including zolmitriptan. It should be noted that migraneurs may be at risk of certain cerebrovascular events.

Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways.

In very rare cases, as with other $5HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. Zolmitriptan Teva 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 Contraindications). 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 Undesirable effects 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 has been reported with combined use of triptans, and Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition, and it may include signs and symptoms such as: mental status changes (e.g. agitation, hallucinations, coma), autonomic instability, (e.g. tachycardia, labile blood-pressure, hyperthermia), neuromuscular aberrations (e.g. hyperrflexia, in-coordination), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Careful observation of the patient is advised, if concomitant treatment with zolmitriptan and an SSRI or SNRI, particularly during treatment initiation and dosage increases (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, if taken during the aura, has not been demonstrated to prevent the migraine headache and therefore Zolmitriptan Teva should be taken during the headache phase of migraine.

Warnings relating to excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with caffeine, ergotamine, dihydroergotamine, paracetamol, metoclopramide, pizotifen, fluoxetine, rifampicin and propranolol and no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Data from healthy subjects suggests there are no pharmacokinetic or clinically significant interactions between 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 Contraindications section 4.3).

Following administration of moclobemide, a specific MAO-A inhibitor, there was a small increase (26%) in AUC for zolmitriptan and a 3 fold increase in AUC of the active metabolite. Therefore, a maximum intake of 5 mg zolmitriptan in 24 hours, is recommended in patients taking a MAO-A inhibitor. Zolmitriptan and moclobenide should not be used together if doses of moclobemide higher than 150 mg b.i.d. are administered.

Following the administration of cimetidine, a general P450 inhibitor, the half life of zolmitriptan was increased by 44% and the AUC increased by 48%. In addition, the half life and AUC of the active, N-desmethylated, metabolite (183C91) were doubled. A maximum dose of 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 (eg ciprofloxacin).

Selegiline (a MAO-B inhibitor) and fluoxetine (a selective serotonin reuptake inhibitor, SSRI) did not result in any pharmacokinetic interaction with zolmitriptan. However, there have been isolated reports describing patients with symptoms compatible with serotonin syndrome (weakness, hyperreflexia, incoordination) following the use of a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRIs) and zolmitriptan. As with other $5HT_{1B/1D}$ receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of zolmitriptan for use in human pregnancy has not been established. Evaluation of experimental animals' studies does not indicate direct teratogenic effects. However, some findings in embryotoxicity studies suggested impaired embryo viability. Administration of zolmitriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation
Studies have shown that zolmitriptan passes into the milk of lactating animals. No data exist for passage of zolmitriptan into human breast milk. Therefore, caution should be exercised when administering zolmitriptan to women who are breast-feeding. Infant exposure should be minimised by avoiding breast feeding for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

In a small group of healthy individuals there was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan. Caution is recommended in patients performing skilled tasks (eg driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack.

4.8 Undesirable effects

Possible undesirable effects are typically transient, tend to occur within four hours of dosing, 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, < 1/10); uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000, including isolated reports), 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:

Nervous system disorders
Common: Abnormalities or disturbances of sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation

Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia
Very rare: Myocardial infarction; Angina pectoris, Coronary vasospasm
Not known: arrhythmias, ventricular tachycardia

Vascular disorders
Uncommon: Slight increase in blood pressure; Transient increases in systemic blood pressure

Gastrointestinal disorders
Common: Abdominal pain; Nausea; Vomiting; Dry mouth
Very rare: Ischaemia or infarction (eg. intestinal ischaemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain.

Renal and Urinary disorders:
Uncommon: Polyuria; Increased urinary frequency
Very rare: Urinary urgency

Musculoskeletal and connective tissue disorders
Common: Muscle weakness; Myalgia

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

General disorders and administration site conditions
Common: Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest

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

4.9 Overdose

Volunteers receiving single oral doses of 50 mg commonly experienced sedation.
The elimination half-life of zolmitriptan tablets is 2.5 to 3 hours, (see Pharmacokinetic Properties Section 5.2) and therefore monitoring of patients after overdose with Zolmitriptan Teva 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 Classification: N02CC03
Zolmitriptan has been demonstrated to be a selective agonist for 5-$HT_{1B/ID}$ receptors mediating vascular contraction. Zolmitriptan has high affinity for human recombinant 5-HT_{IB} and 5-HT_{ID} receptors, and modest affinity for 5-HT_{IA} receptors. Zolmitriptan has no significant affinity or pharmacological activity at other 5-HT receptor subtypes (5-HT_2, 5-HT_3, 5-HT_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 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 is consistently effective in migraine with or without aura and in menstrually associated migraine.
One controlled clinical trial in 696 adolescents with migraine failed to demonstrate superiority of zolmitriptan tablets at doses of 2.5 mg, 5 mg and 10 mg over placebo. Efficacy was not demonstrated.

5.2 Pharmacokinetic properties

Zolmitriptan is rapidly and well absorbed (at least 64%) after oral administration to man. The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (the N-desmethyl metabolite) which is also a $5HT_{1B/1D}$ receptor agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan.
In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite, the Ndesmethyl 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 achived 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 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 Teva. 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 iv administration is 2.4 L/kg. Plasma protein binding of zolmitriptan and the N-desmethyl metabolite is low (approximately 25%). The mean elimination half-life of zolmitriptan is 2.5 to 3 hours. The half-lives of its metabolites are similar, suggesting their elimination is formation-rate limited.
Renal clearance of zolmitriptan and all its metabolites is reduced (7-8 fold) in patients with moderate to severe renal impairment compared to healthy subjects, although the AUC of the parent compound and the active metabolite were only slightly higher (16 and 35% respectively) with a 1 hour increase in half-life to 3 to 3.5 hours. These parameters are within the ranges seen in healthy volunteers.
The metabolism of zolmitriptan is reduced in hepatic impairment in proportion to the extent of the impairment. Zolmitriptan AUC and Cmax were increased by 226% and 50%, respectively and the half life was prolonged to 12 h in subjects with severe liver disease compared to healthy subjects. Exposure to the metabolites, including the active metabolite was reduced.
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

Core
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate (Type A)
Magnesium stearate

Coating
Opadry II yellow 85F92536 which contains:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

2, 3, 6, 12 or 18 tablets in Al/Al blister.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542 DR Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/68/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th February 2009

10 DATE OF REVISION OF THE TEXT

March 2012