Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rizatriptan Teva 10 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mg orodispersible tablet contains 14.53 mg of rizatriptan benzoate (corresponding to 10 mg of rizatriptan).

Excipients:

Each 10 mg orodispersible tablet contains 2.0 mg of aspartame

Each 10 mg orodispersible tablet contains 110.20 mg of lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

10 mg orodispersible tablets are white to off white, round, flat tablets with bevelled edges, embossed with ‘IZ’ on one side and ‘10’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute treatment of the headache phase of migraine attacks, with or without aura.

4.2 Posology and method of administration

General

Rizatriptan Teva should not be used prophylactically.

Rizatriptan Teva orodispersible tablets need not be taken with liquid.

The orodispersible tablet is packaged in an aluminium blister. Patients should be instructed not to remove the orodispersible tablet from the blister until just prior to dosing. The orodispersible tablet should then be removed from the aluminium blister with dry hands and then placed on the tongue, where it will dissolve and be swallowed with the saliva.

The orodispersible tablet 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.

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

<u>Adults 18 years of age and older</u>

The recommended dose is 10 mg.

Redosing: doses should be separated by at least two hours; no more than two doses should be taken in any 24-hour period.

− *for headache recurrence within 24 hours*: if headache returns after relief of the initial attack, one further dose may be taken. The above dosing limits should be observed.

− *after non-response*: the effectiveness of a second dose for treatment of the same attack, when an initial dose is ineffective, has not been examined in controlled trials. Therefore, if a patient does not respond to the first dose, a second dose should not be taken for the same attack.

Clinical studies have shown that patients who do not respond to treatment of an attack are still likely to respond to treatment for subsequent attacks.

Some patients should receive 5 mg of Rizatriptan Teva if it is available, in particular the following patient groups:

− patients on propranolol. Administration of rizatriptan should be separated by at least two hours from administration of propranolol. (See section 4.5)

− patients with mild or moderate renal insufficiency,

− patients with mild to moderate hepatic insufficiency.

Paediatric patients

Children (under 12 years of age)

The use of Rizatriptan Teva in patients under 12 years of age is not recommended. There are no data available on the use of rizatriptan in children under 12 years of age.

Adolescents (12-17 years of age)

The use of Rizatriptan Teva in patients under 18 years of age is not recommended. Safety and effectiveness of rizatriptan in adolescent patients have not been established.

Patients older than 65 years

The safety and effectiveness of rizatriptan in patients older than 65 years have not been systematically evaluated.

4.3 Contraindications

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

Concurrent administration of monoamine oxidase (MAO) inhibitors or use within two weeks of discontinuation of MAO inhibitor therapy. (See section 4.5).

Rizatriptan Teva is contra-indicated in patients with severe hepatic or severe renal insufficiency.

Rizatriptan Teva is contra-indicated in patients with a previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Moderately severe or severe hypertension, or untreated mild hypertension.

Established coronary artery disease, including ischaemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischaemia), signs and symptoms of ischaemic heart disease, or Prinzmetal's angina.

Peripheral vascular disease.

Concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5-$HT_{1B/1D}$ receptor agonists. (See section 4.5).

4.4 Special warnings and precautions for use

Rizatriptan Teva should only be administered to patients in whom a clear diagnosis of migraine has been established. Rizatriptan Teva should not be administered to patients with basilar or hemiplegic migraine.

Rizatriptan Teva should not be used to treat 'atypical' headaches, i.e. those that might be associated with potentially serious medical conditions, (e.g. CVA, ruptured aneurysm) in which cerebrovascular vasoconstriction could be harmful.

Rizatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see section 4.8). Where such symptoms are thought to indicate ischaemic heart disease, no further dose should be taken and appropriate evaluation should be carried out.

As with other 5-$HT_{1B/1D}$ receptor agonists, rizatriptan should not be given, without prior evaluation, to patients in whom unrecognised cardiac disease is likely or to patients at risk for coronary artery disease (CAD) [e.g. patients with hypertension, diabetics, smokers or users of nicotine substitution therapy, men over 40 years of age, post-menopausal women, patients with bundle branch block, and those with strong family history for CAD]. Cardiac evaluations 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 when 5-HT_1 agonists have been administered. Those in whom CAD is established should not be given Rizatriptan Teva. (See section 4.3)

5-$HT_{1B/1D}$ receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischaemia or infarction have been reported with 5-$HT_{1B/1D}$ receptor agonists including rizatriptan (see section 4.8).

Other 5-$HT_{1B/1D}$ agonists (e.g., sumatriptan) should not be used concomitantly with Rizatriptan Teva (see section 4.5).

It is advised to wait at least six hours following use of rizatriptan before administering ergotamine-type medicinal products, (e.g. ergotamine, dihydro-ergotamine or methysergide). At least 24 hours should elapse after the administration of an ergotamine-containing preparation before rizatriptan is given. Although additive vasospastic effects were not observed in a clinical pharmacology study in which 16 healthy males received oral rizatriptan and parenteral ergotamine, such additive effects are theoretically possible, (see section 4.3).

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 noradrenaline reuptake inhibitors (SNRIs). These reactions can be severe. If concomitant treatment with rizatriptan 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).

Undesirable effects may be more common during concomitant use of triptans (5-$HT_{1B/1D}$ agonists) and herbal preparations containing St John's wort (*Hypericum perforatum*).

Angioedema (e.g. facial oedema, tongue swelling and pharyngeal oedema) may occur in patients treated with triptans, among which rizatriptan. If angioedema of the tongue or pharynx occurs, the patient should be placed under medical supervision until symptoms have resolved. Treatment should promptly be discontinued and replaced by an agent belonging to another class of drugs.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Phenylketonurics: Rizatriptan Teva orodispersible tablets contain aspartame, a source of phenylalanine. May be harmful for people with phenylketonuria.

The potential for interaction should be considered when rizatriptan is administered to patients taking CYP 2D6 substrates (see section 4.5)

Medication overuse headache (MOH)

Prolonged use of any 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 MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

4.5 Interaction with other medicinal products and other forms of interaction

Ergotamine, ergot derivatives (including methysergide), other 5 HT $_{1B/1D}$ receptor agonists: Due to an additive effect, the concomitant use of rizatriptan and ergotamine, ergot derivatives (including methysergide), or other 5 $HT_{1B/1D}$ receptor agonists (e.g. sumatriptan, zolmitriptan, naratriptan) increase the risk of coronary artery vasoconstriction and hypertensive effects. This combination is contraindicated (see section 4.3).

Monoamine oxidase inhibitors: Rizatriptan is principally metabolised via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite were increased by concomitant administration of a selective, reversible MAO-A inhibitor. Similar or greater effects are expected with non-selective, reversible (e.g. linezolid) and irreversible MAO inhibitors. Due to a risk of coronary artery vasoconstriction and hypertensive episodes, administration of Rizatriptan Teva to patients taking inhibitors of MAO is contraindicated. (See section 4.3)

Beta-blockers: Plasma concentrations of rizatriptan may be increased by concomitant administration of propranolol. This increase is most probably due to first-pass metabolic interaction between the two drugs, since MAO-A plays a role in the metabolism of both rizatriptan and propranolol. This interaction leads to a mean increase in AUC and C_{max} of 70-80%. In patients receiving propranolol, the 5 mg dose of Rizatriptan Teva should be used. (See section 4.2)

In a drug-interaction study, nadolol and metoprolol did not alter plasma concentrations of rizatriptan.

Selective Serotonin Reuptake Inhibitors (SSRIs) /Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Serotonin Syndrome: 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 noradrenaline reuptake inhibitors (SNRIs) and triptans (see section 4.4).

In vitro studies indicate that rizatriptan inhibits cytochrome P450 2D6 (CYP 2D6). Clinical interaction data are not available. The potential for interaction should be considered when rizatriptan is administered to patients taking CYP 2D6 substrates.

4.6 Fertility, pregnancy and lactation

Use during pregnancy

The safety of rizatriptan for the use in human pregnancy has not been established. Animal studies do not indicate harmful effects at dose levels that exceed therapeutic dose levels with respect to the development of the embryo or foetus, or the course of gestation, parturition and post-natal development.

Because animal reproductive and developmental studies are not always predictive of human response Rizatriptan Teva should be used during pregnancy only if clearly needed.

Use during lactation

Studies in rats indicated that very high milk transfer of rizatriptan occured. Transient, very slight decreases in pre-weaning pup body weights were observed only when the mother's systemic exposure was well in excess of the maximum exposure level for humans. No data exist in humans.

Therefore, caution should be exercised when administering rizatriptan 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

Migraine or treatment with Rizatriptan Teva may cause somnolence in some patients. Dizziness has also been reported in some patients receiving rizatriptan. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of Rizatriptan Teva.

4.8 Undesirable effects

Rizatriptan was evaluated in over 3,600 patients for up to one year in controlled clinical studies. The most common undesirable effects evaluated in clinical studies were dizziness, somnolence, and asthenia/fatigue. The following undesirable effects have been evaluated in clinical studies and/or reported in post marketing experience:

(*Very common* [≥1/10]; *Common* [≥1/100 to <1/10]; *Uncommon* [≥1/1000 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]).

Immune system disorders:

Not known: hypersensitivity reaction, anaphylaxis/anaphylactoid reaction.

Psychiatric disorders:

Uncommon: disorientation, insomnia, nervousness.

Nervous system disorders:

Common: dizziness, somnolence, paresthesia, headache, hypaesthesia, decreased mental acuity, tremor.

Uncommon: ataxia, vertigo

Rare: syncope, dysgeusia/ bad taste, serotonin syndrome

Not known: seizure

Eye disorders:

Uncommon: blurred vision.

Cardiac disorders:

Common: palpitation, tachycardia

Rare: Myocardial ischaemia or infarction, cerebrovascular accident. Most of these adverse reactions have been reported in patients with risk factors predictive of coronary artery disease.

Not known: arrhythmia, bradycardia.

Vascular disorders:

Common: hot flushes/flashes

Uncommon: hypertension.

Not known: peripheral vascular ischaemia.

Respiratory, thoracic and mediastinal disorders:

Common: pharyngeal discomfort, dyspnoea

Rare: wheezing.

Gastrointestinal disorders:

Common: nausea, dry mouth, vomiting, diarrhoea

Uncommon: thirst, dyspepsia.

Not known: ischemic colitis.

Skin and subcutaneous tissue disorders:

Common: flushing, sweating

Uncommon: pruritus, urticaria

Rare: angioedema (e.g. facial oedema, tongue swelling, pharyngeal oedema), rash, toxic epidermal necrolysis (for angioedema see also section 4.4).

Musculoskeletal, connective tissue and bone disorders:

Common: regional heaviness

Uncommon: neck pain, regional tightness, stiffness, muscle weakness.

Rare: facial pain.

Not known: myalgia.

General disorders and administration site conditions:

Common: asthenia/fatigue, pain in abdomen or chest.

Investigations:
Not known: ECG abnormalities.

4.9 Overdose

Rizatriptan 40 mg (administered as either a single tablet dose or as two doses with a two-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours). A third-degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25 year-old male, experienced transient dizziness, syncope, incontinence, and a five-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastro-intestinal decontamination, (e.g. gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with Rizatriptan Teva. Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

The effects of haemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin ($5HT_1$) agonists, ATC-code: N02C C04

Mechanism of action: Selective serotonin ($5HT_{1B/1D}$) agonists

Rizatriptan binds selectively with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors and has little or no effect or pharmacological activity at 5-HT_2, 5-HT_3; adrenergic $alpha_1$, $alpha_2$ or beta; D_1, D_2, dopaminergic, histaminic H_1; muscarinic; or benzodiazepine receptors.

The therapeutic activity of rizatriptan in treating migraine headache may be attributed to its agonist effects at 5-HT_{1B} and 5-HT_{1D} receptors on the extracerebral intracranial blood vessels that are thought to become dilated during an attack and on the trigeminal sensory nerves that innervate them. Activation of these 5-HT_{1B} and 5-HT_{1D} receptors may result in constriction of pain-producing intracranial blood vessels and inhibition of neuropeptide release that leads to decreased inflammation in sensitive tissues and reduced central trigeminal pain signal transmission.

Pharmacodynamic effects

The efficacy of rizatriptan in the acute treatment of migraine attacks was established in two multicentre, randomised, placebo-controlled trials. In one study (n=311), by two hours post-dosing, relief rates in patients treated with rizatriptan were approximately 66% for rizatriptan 5 mg and 10 mg, compared to 47% in the placebo group. In a larger study (n=547), by two hours post-dosing, relief rates were 59% in patients treated with rizatriptan 5 mg, and 74% after 10 mg, compared to 28% in the placebo group. Rizatriptan also relieved the disability, nausea, photophobia, and phonophobia which accompanied the migraine episodes. A significant effect on pain relief was observed as early as 30 minutes post-dosing in one of the two clinical trials for the 10 mg dose (see section 5.2 *Absorption*).

Based on studies with rizatriptan tablets, rizatriptan remains effective in treating menstrual migraine, i.e. migraine that occurs within 3 days before or after the onset of menses.

Rizatriptan Teva orodispersible tablets enables migraine patients to treat their migraine attacks without having to swallow liquids. This may allow patients to administer their medicinal product earlier, for example, when liquids are not available, and to avoid possible worsening of gastrointestinal symptoms by swallowing liquids.

5.2 Pharmacokinetic properties

Absorption

Rizatriptan is rapidly and completely absorbed following oral administration.

The mean oral bioavailability of the orodispersible tablet is approximately 40-45%, and mean peak plasma concentration (C_{max}) is reached in approximately 1.6 - 2.5 hours (T_{max}).

Effect of food: The effect of food on the absorption of rizatriptan from the orodispersible tablet has not been studied. For the rizatriptan tablets, T_{max} is delayed by approximately 1 hour when the tablets are administered in the fed state. A further delay in the absorption of rizatriptan may occur when the orodispersible tablet is administered after meals.

Distribution

Rizatriptan is minimally bound (14%) to plasma proteins. The volume of distribution is approximately 140 litres in male subjects, and 110 litres in female subjects.

Biotransformation

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not pharmacologically active. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-$HT_{1B/1D}$ receptors, is formed to a minor degree, but does not contribute significantly to the pharmacodynamic activity of rizatriptan. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites include the N-oxide, the 6-hydroxy compound, and the sulphate conjugate of the 6-hydroxy metabolite. None of these minor metabolites is pharmacologically active. Following oral administration of ^{14}C-labelled rizatriptan, rizatriptan accounts for about 17% of circulating plasma radioactivity.

Elimination

Following intravenous administration, AUC in men increases proportionally and in women near-proportionally with the dose over a dose range of 10-60 µg/kg. Following oral administration, AUC increases near-proportionally with the dose over a dose range of 2.5- 10 mg. The plasma half-life of rizatriptan in males and females averages 2-3 hours. The plasma clearance of rizatriptan averages about 1,000-1,500 ml/min in males and about 900-1,100 ml/min in females; about 20-30% of this is renal clearance. Following an oral dose of ^{14}C-labelled rizatriptan, about 80% of the radioactivity is excreted in urine, and about 10% of the dose is excreted in faeces. This shows that the metabolites are excreted primarily via the kidneys.

Consistent with its first pass metabolism, approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite. No more than 1% is excreted in urine as the active N-monodesmethyl metabolite.

If rizatriptan is administered according to the maximum dosage regimen, no accumulation of the active substance in the plasma occurs from day to day.

Characteristics in patients

The following data are based on studies with a tablet formulation.

Patients with a migraine attack: A migraine attack does not affect the pharmacokinetics of rizatriptan.

Gender: The AUC of rizatriptan (10 mg orally) was about 25% lower in males as compared to females, C_{max} was 11% lower, and T_{max} occurred at approximately the same time. This apparent pharmacokinetic difference was of no clinical significance.

Elderly: The plasma concentrations of rizatriptan observed in elderly subjects (age range 65 to 77 years) after tablet administration were similar to those observed in young adults.

Hepatic impairment (Child-Pugh's score 5-6): Following oral tablet administration in patients with hepatic impairment caused by mild alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar to those seen in young male and female subjects. A significant increase in AUC (50%) and C_{max} (25%) was observed in patients with moderate hepatic impairment (Child-Pugh's score 7). Pharmacokinetics were not studied in patients with Child-Pugh's score >7 (severe hepatic impairment).

Renal impairment: In patients with renal impairment (creatinine clearance 10-60 ml/min/1.73 m^2), the AUC of rizatriptan after tablet administration was not significantly different from that in healthy subjects. In haemodialysis patients (creatinine clearance <10 ml/min/1.73 m^2), the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. The maximal plasma concentration of rizatriptan in patients with all degrees of renal impairment was similar to that in healthy subjects.

5.3 Preclinical safety data

Preclinical data indicate no risk for humans based on conventional studies of repeat dose toxicity, genotoxicity, carcinogenic potential, reproductive and developmental toxicity, safety pharmacology, and pharmacokinetics and metabolism.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Maize starch,
Mannitol (E421),
Pregelatinized starch (maize),
Aspartame (E951),
Peppermint flavour,
Sillica colloidal anhydrous,
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

OPA/Aluminium/PVC-Aluminium perforated unit dose blisters in cartons of 2, 3, 6, 12, 18, 28 or 30 orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/106/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 February 2010

10 DATE OF REVISION OF THE TEXT

March 2012