Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zolmitriptan Renantos 2.5 mg orodispersible films

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mg Zolmitriptan Renantos orodispersible film contains 2.5 mg zolmitriptan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible film.

White, rectangular (size 3 cm^2) orodispersible film.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The acute treatment of migraine headache with or without aura.

It is not a treatment to prevent migraine attacks.

4.2 Posology and method of administration

Posology
The recommended dose of Zolmitriptan to treat a migraine attack is 2.5 mg. Zolmitriptan Renantos should be taken as soon as possible after the onset of the migraine, but are still effective if taken at a later time.

If symptoms should return within 24 hours following an initial response, a second dose of Zolmitriptan Renantos orodispersible films may be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose. If a patient does not respond to the first dose, it is unlikely that a second dose will be of benefit in the same attack.

If a patient does not achieve satisfactory relief with 2.5 mg doses, for subsequent attacks 5 mg doses of zolmitriptan could be considered. Caution is advised due to an increase 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 Renantos should be taken in any 24 hour period.

Patients Aged Over 65 years
Safety and efficacy of zolmitriptan in individuals aged over 65 years has not been established. Use of Zolmitriptan Renantos 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 is required for patients with a creatinine clearance > 15 ml/min (see sections 4.3 and 5.2).

Interactions that necessitate a dosage adjustment (see section 4.5)
A maximum dosage of 5 mg zolmitriptan within 24 hours is recommended for patients taking MAO-A inhibitors.
A maximum dosage of 5 mg zolmitriptan within 24 hours is recommended for patients taking cimetidine.
A maximum dosage of 5 mg zolmitriptan within 24 hours is recommended for patients taking specific CYP-1A2 inhibitors, e.g. fluvoxamine and quinolones (e.g. ciprofloxacin).

Paediatric population
Safety and efficacy of zolmitriptan in paediatric patients has not been studied. Use of Zolmitriptan Renantos orodispersible films 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 Renantos orodispersible films in adolescents is therefore not recommended.

Method of administration
A drink of water is not required when taking Zolmitriptan Renantos orodispersible films. The orodispersible film rapidly dissolves when placed on the tongue and is swallowed with the saliva. This dosage form is indicated in situations in which no fluids are available or when fluids consumption may enhance the nausea and vomiting symptoms associated with migraine. This dosage form is helpful to adult patients with swallowing disorders (risk of aspiration, difficulty in swallowing bulky tablets).
This medicinal product is packaged in two different packaging materials (see section 6.5, peelable and non-peelable). Each packaging material results in a different opening modality of the sachet: peel apart and tear-off, respectively. Depending on the packaging, the leaflet will have either one of the following two opening instructions:

(1)
Remove from each individual sachet in the following way:
1. Do not cut the sachet,
2. Open very carefully,
3. Open only at the tear tag,
4. Tear off slowly,
5. Check the film for damage,
6. Use only undamaged films.
7. Take immediately after opening the sachet.

(2)
Remove the film from its individual sachet in the following way:
1. Do not cut the sachet
2. Open very carefully
3. Open only using the tear flap
4. Slowly peel both sides of the packaging apart
5. Check the film for damage
6. Use only undamaged films
7. Take immediately after opening the sachet.

The mouth should be empty before placing Zolmitriptan Renantos orodispersible films on the tongue. Zolmitriptan Renantos orodispersible film should be placed on the tongue with a dry finger. The film disintegrates without water in few seconds in saliva which can be subsequently swallowed.
Use only undamaged sachet.

4.3 Contraindications

Hypersensitive to zolmitriptan or to any of the excipients.

Moderate or severe hypertension or inadequately controlled mild hypertension.

Since this substance class (5-$HT_{1B/1D}$ receptor agonists) is associated with the occurrence of coronary vasospasm, patients with coronary heart disease have been excluded from clinical investigations. Consequently, Zolmitriptan Renantos orodispersible films should not be used in patients with a history of myocardial infarction or who are suffering from coronary heart disease, coronary spasms (Prinzmetal's angina) or arterial occlusive disease or in whom symptoms compatible with coronary heart disease have been observed.

The concurrent use of zolmitriptan and ergotamine, ergotamine derivatives (including methysergide), sumatriptan, naratriptan and other 5-$HT_{1B/1D}$ receptor agonists is contraindicated (see section 4.5).

Zolmitriptan may not be used in patients with a history of cerebrovascular accident (CVA), stroke or transient ischaemic attacks (TIA).

Zolmitriptan is contraindicated in patients with a creatinine clearance < 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 treatments, the possibility of other potentially serious neurological disorders must be ruled out before the headache is treated in patients who have not yet been diagnosed with migraine or in migraine patients with atypical symptoms.

Zolmitriptan is not indicated for the treatment of hemiplegic migraine, basilar migraine or ophthalmoplegic migraine.

Strokes and other cerebrovascular events have been reported in patients treated with 5-$HT_{1B/1D}$ receptor agonists. It should be noted, however, that a risk for certain cerebrovascular events exists in any case for migraine patients.

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

As with other 5-$HT_{1B/1D}$ receptor agonists, coronary spasms, angina pectoris and myocardial infarctions have been reported in very rare cases.
Zolmitriptan Renantos orodispersible films should not be prescribed to patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus, hereditary condition) without first being investigated for a pre-existing cardiovascular disorder (see section 4.3).
Particular consideration should be given in this respect to postmenopausal women and men over 40 years of age with these risk factors. Despite these investigations, it is still possible that not every patient with heart disease will be identified, and serious cardiac events have occurred in very rare cases in patients without underlying cardiovascular disease.
As with other 5-$HT_{1B/1D}$ receptor agonists, a sensation of heaviness, pressure or constriction in the heart area has also been reported after the administration of zolmitriptan (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 recommended doses for zolmitriptan should not be exceeded.

Undesirable effects can occur more frequently during the concurrent use of triptans and herbal preparations containing St. John's Wort (Hypericum perforatum).

A serotonin syndrome (including an altered mental status, autonomic symptoms and neuromuscular abnormalities) has also been reported after the concomitant use of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs). These reactions can be serious.
If concurrent treatment with zolmitriptan and an SSRI or SNRI is clinically indicated, careful monitoring of the patient is recommended, particularly at the start of treatment, in the event of a dosage increase or at the start of other serotonergic medication (see section 4.5).

Prolonged use of painkillers of any kind for headaches can increase their frequency. If this occurs, or is suspected, medical advice should be sought and the treatment suspended.
Excessive use of medicines should be considered in patients who suffer frequent or daily headaches despite (or because of) the regular administration of headache tablets.

4.5 Interaction with other medicinal products and other forms of interaction

Studies investigating interactions with caffeine, ergotamine, dihydroergotamine, paracetamol, metoclopramide, pizotifen, fluoxetine, rifampicin and propranolol have not shown any clinically relevant changes in the pharmacokinetics of zolmitriptan or its active metabolite.

Data from healthy subjects suggest there are no pharmacokinetic or clinically significant interactions between Zolmitriptan Renantos orodispersible films and ergotamine. However, the increased risk of coronary vasospasm is a theoretical possibility and concomitant use is contraindicated. It is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering Zolmitriptan Renantos orodispersible films. Conversely it is advised to wait at least six hours following use of Zolmitriptan Renantos orodispersible films before administering any ergotamine preparation (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 an MAO-A inhibitor. These medicinal products should not be taken together if a dosage higher than 150 mg moclobemide twice daily is taken.

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 Renantos orodispersible films in 24 hours is recommended in patients taking cimetidine. Based on the overall interaction profile, an interaction with inhibitors of the cytochrome P450 isoenzyme CYP1A2 cannot be excluded. Therefore, the same dosage reduction is recommended with compounds of this type, such as fluvoxamine and the quinolone antibiotics (e.g. ciprofloxacin).

Although selegiline (an MAO-B inhibitor) and fluoxetine (an SSRI) have not shown any pharmacokinetic interactions with zolmitriptan, there have been reports of patients showing symptoms resembling a serotonin syndrome (including an altered mental status, autonomic symptoms and neuromuscular abnormalities) after the administration of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) and triptans (see section 4.4).

As with other 5-$HT_{1B/1D}$ receptor agonists zolmitriptan may delay the absorption of other medicines.

Concomitant administration of other 5-HT1B/1D agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other 5-HT1B/1D agonists should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of use of this preparation has not been confirmed in pregnancy. While the evaluations of animal study results have not shown any evidence of direct teratogenic effects, embryotoxicity investigations have shown evidence of a possible impairment of embryo survivability. Zolmitriptan should only be used in pregnancy if the benefits to the mother justify potential 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.

In order to minimise the absorption of zolmitriptan by the infant, the mother should not breast feed for up to 24 hours after taking zolmitriptan.

4.7 Effects on ability to drive and use machines

Zolmitriptan Renantos has no or negligible influence on the ability to drive or to use machines.

There was no significant impairment of performance of psychomotor tests in a small group of healthy individuals with doses up to 20 mg zolmitriptan.

However it should be taken into account that somnolence may occur.

4.8 Undesirable effects

Possible undesirable effects of zolmitriptan are usually transient, normally occur within 4 hours of administration, are no more frequent following repeated administration and resolve spontaneously without the need for additional treatment.

The frequencies of undesirable effects are based on the following categories: 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).

The undesirable effects are listed in order of decreasing severity within the frequencies.

The following adverse events have been observed after the administration of zolmitriptan:

System Organ Class	**Frequency**	**Undesirable Effect**
Immune system disorders	Rare	Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions
Nervous system disorders	Common	Abnormalities or disturbances of sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Very rare	Myocardial infarction; Angina pectoris; Coronary vasospasm
Vascular disorders	Uncommon	Slight increases in blood pressure; Transient increases in systemic blood pressure

Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth
	Very rare	Ischaemia or infarction (e.g. intestinal ischaemia, intestinal infarction, splenic infarction) which may present as bloody diarrhoea or abdominal pain
Musculoskeletal and connective tissue disorders	Common	Muscle weakness; Myalgia
Renal and Urinary disorders	Uncommon	Polyuria; Increased urinary frequency
	Very rare	Urinary urgency
General disorders and administration site disorders	Common	Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

Some of the symptoms could be part of the migraine attack itself.

4.9 Overdose

Volunteers frequently reported sedation after taking a single dose of 50 mg. The elimination half-life of zolmitriptan is 2.5 to 3 hours, (see section 5.2) and therefore monitoring of patients after overdose with Zolmitriptan Renantos orodispersible films 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: analgesics; antimigraine preparations; selective serotonin (5HT1) agonists
ATC code: N02CC03

Zolmitriptan has been shown to be a selective agonist of the 5-$HT_{1B/1D}$ receptor that mediates vasoconstriction. Zolmitriptan has a high affinity for human recombinant 5-HT_{1B} and 5-HT_{1D} receptors and a moderate affinity for 5-HT_{1A} receptors. Zolmitriptan has not significant affinity or pharmacological activity on other 5-HT receptor subtypes (5-HT_2, 5-HT_3, 5-HT_4) or adrenergic, histaminergic, muscarinergic or dopaminergic receptors.

In animal studies the administration of zolmitriptan caused vasoconstriction in the area supplied by the carotid artery. The results of animal studies also suggest that zolmitriptan suppresses the activity of the trigeminal nerve, both centrally and peripherally, by inhibiting the release of neuropeptides (calcitonin gene related peptide [CGRP], vasoactive intestinal peptide [VIP] and substance P).

In clinical investigations with the traditional zolmitriptan tablets, the onset of action occurred within an hour of administration, followed, after 2 to 4 hours, by an increase in efficacy against headaches and other migraine symptoms such as nausea, sensitivity to light and noise.

Zolmitriptan is equally effective in migraines with or without an aura and in migraines associated with menstruation. Since it has not been shown that the administration of zolmitriptan during the aura prevents the occurrence of migraine headaches, Zolmitriptan Renantos orodispersible films should not be taken until the headache phase of the 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%) in man. The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (183C91, the N-desmethyl metabolite) which is also a $5\text{-HT}_{IB/1D}$ agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan.

In healthy subjects taking single doses of 2.5 - 50 mg zolmitriptan, the AUC and C_{max} of zolmitriptan and its active metabolite, the N-desmethyl metabolite, were proportional to the dose over this range. Zolmitriptan is rapidly absorbed. In healthy subjects, 75 % of C_{max} is achieved within one hour.
Thereafter the plasma concentration of zolmitriptan remains roughly at this level over a period of 4 -5 hours. Zolmitriptan absorption is not affected by the presence of food. There is no evidence of accumulation on multiple dosing of zolmitriptan.

Compared to a migraine-free phase, the plasma concentration of zolmitriptan and its metabolite is lower during a migraine in the first 4 hours after administration of the preparation, which suggests that absorption is delayed. This is compatible with the delayed gastric emptying observed during the migraine attack.

Clinical pharmacology data show that the t_{max} for zolmitriptan orodispersible formulations are in the range of 0.6h – 5h. The t_{max} for the active metabolite is about 3h (median value).

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. There are three major metabolites: the indole acetic acid, (the major metabolite in plasma and urine), the N-oxide and N-desmethyl analogues. The N-desmethylated metabolite (183C91) is the only active metabolite. Plasma concentrations of 183C91 are approximately half those of the parent drug, hence it would therefore be expected to contribute to the therapeutic action of zolmitriptan.
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 is low (approximately 25%). The mean elimination half-life of zolmitriptan is 2.5 to 3 hours. The half-lives of its metabolites are similar, suggesting their elimination is formation-rate limited.

Renal clearance of zolmitriptan and all its metabolites is reduced (7 to 8 fold) in patients with moderate to severe renal impairment compared to healthy subjects, although the AUC of the parent compound and the active metabolite were only slightly higher (16 and 35% respectively) with a 1 hour increase in half-life to 3 to 3.5 hours. These parameters are within the ranges seen in healthy volunteers.

The metabolism of zolmitriptan is reduced in hepatic impairment in proportion to the extent of impairment. A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and Cmax were increased by 94% and 50% respectively in patients with moderate liver disease and by 226% and 47% in patients with severe liver disease compared with healthy volunteers, while the half life was prolonged up to 12 hours.

The burden resulting from 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

In preclinical studies on acute and chronic toxicity, toxic effects were observed only at dosages well above the human maximum therapeutic dosage.

The results of in-vitro and in-vivo genotoxicity tests show that no genotoxic effects of zolmitriptan are expected under conditions of clinical use.

Long-term studies investigating the tumorigenic potential in mice and rats did not find any tumours of relevance to clinical use.
Like other 5-$HT_{1B/1D}$ receptor agonists zolmitriptan also binds to melanin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyvinyl alcohol
Macrogol 4000
Macrogol 400
Rice starch
Acesulfame potassium
Orange flavour SN027512 (contains Flavouring, Butylated Hydroxy Anisole E320)
Titanium dioxide (E171)
Glutathione

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product doesn’t require any special storage conditions.

6.5 Nature and contents of container

Zolmitriptan Renantos orodispersible films are packed in a sachet which will be opened and removed before administration.

The sachet material is of two types:

– non peelable: two foils made of paper-PE-Aluminium-Ionomer
– peelable: one foil made of paper-PE-Aluminium-Ionomer and one foil made of paper-ethylene copolymer-Aluminium-adhesive-PE (Peelable layer).

Pack sizes of 2, 3, 6, 10, 12 or 18 orodispersible films.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Renantos Pharmavertriebsges. mbH
Beethovenstr. 10,
89340 Leipheim
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1695/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st June 2012

10 DATE OF REVISION OF THE TEXT