

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan Sandoz smelttablet, 2,5 mg, orodispergeerbare tabletten
Zolmitriptan Sandoz smelttablet, 5 mg, orodispergeerbare tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[2.5 mg]

Each orodispersible tablet contains 2.5 mg of zolmitriptan.

Excipients with known effect

Each orodispersible tablet contains up to 25 ng of sulphites and 2.5 mg of aspartame.

[5 mg]

Each orodispersible tablet contains 5 mg of zolmitriptan.

Excipients with known effect

Each orodispersible tablet contains up to 50 ng of sulphites and 5 mg of aspartame.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

[2.5 mg]

White, round, flat orodispersible tablets with 'ZMT 2.5' debossed on one side.

[5 mg]

White, round, flat orodispersible tablets with 'ZMT 5' debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Nationally completed name] is indicated in adults aged 18 years and older for acute treatment of migraine headache with or without aura.

4.2 Posology and method of administration

Posology

The recommended dose of [Nationally completed name] orodispersible tablets to treat a migraine attack is 2.5 mg. It is advisable that [Nationally completed name] is taken as early as possible after the onset of migraine headache but it is also effective if taken at a later stage.

If symptoms of migraine should recur within 24 hours following an initial response, a second dose may be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose. If a

patient does not respond to the first dose, it is unlikely that a second dose will be of benefit in the same attack.

If a patient does not achieve satisfactory relief with 2.5 mg doses, for subsequent attacks 5 mg doses of [Nationally completed name] could be considered.

The total daily intake should not exceed 10 mg. Not more than 2 doses of [Nationally completed name] should be taken in any 24 hour period.

[Nationally completed name] is not indicated for prophylaxis of migraine.

Paediatric population

- *Use in Children (under 12 years of age)*
The safety and efficacy of zolmitriptan in children aged birth to < 12 years have not been established. No data are available. Use of [Nationally completed name] in children is therefore not recommended.
- *Adolescents (12 - 17 years of age)*
The efficacy of zolmitriptan in adolescents aged 12 to 17 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made. Use of [Nationally completed name] 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 [Nationally completed name] in the elderly is therefore not recommended.

Patients with hepatic impairment

The metabolism of zolmitriptan is reduced in patients with hepatic impairment (see section 5.2). For patients with moderate or severe hepatic impairment, a maximum dose of 5 mg in 24 hours is recommended. However, no dose adjustment is required for patients with mild hepatic impairment.

Patients with renal impairment

No dose adjustment required in patients with a creatinine clearance of more than 15 ml/min. (see sections 4.3 and 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).

Method of administration

The orodispersible 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 [Nationally completed name] can occur which may delay onset of action.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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, ergotamine derivatives (including methysergide), sumatriptan, naratriptan and other 5HT_{1B/1D} receptor agonists with zolmitriptan is contraindicated (see 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 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.

Serotonin syndrome has been reported with combined use of triptans and serotonergic medicinal products, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Serotonin syndrome is a potentially life-threatening condition and diagnosis is likely when (in presence of a serotonergic agent) one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature $>38^{\circ}\text{C}$ and inducible or ocular clonus

Careful observation of the patient is advised if concomitant treatment with zolmitriptan and an SSRI or SNRI is necessary, particularly during treatment initiation and dose increases (see section 4.5). Withdrawal of the serotonergic medicinal product usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

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.

[Nationally completed name] contains sodium, sulphites and aspartame

This medicinal product contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.

Sulphites may rarely cause severe hypersensitivity reactions and bronchospasm.

[2.5 mg]

This medicinal product contains 2.5 mg of aspartame in each orodispersible tablet. Aspartame is a source of phenylalanine. This medicinal product may be harmful for people with phenylketonuria.

[5 mg]

This medicinal product contains 5 mg of aspartame in each orodispersible tablet. Aspartame is a source of phenylalanine. This medicinal product 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 medicinal products 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 (N-desmethylzolmitriptan) 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 dose 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).

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (*Hypericum perforatum*).

As with other 5HT_{1B/1D} receptor agonists, zolmitriptan could delay the absorption of other medicinal products.

Concomitant administration of other 5HT_{1B/1D} agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other 5HT_{1B/1D} agonists should be avoided.

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal 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.

Breast-feeding

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

Zolmitriptan has no or negligible influence on the 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 (e.g. 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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:

| System Organ Class | Common | Uncommon | Rare | Very rare |
|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immune system disorders | | | Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions | |
| Nervous system disorders | Abnormalities or disturbances or sensation; Dizziness; Headache; Hyperaesthesia; Paraesthesia; Somnolence; Warm sensation | | | |
| Cardiac disorders | Palpitations | Tachycardia | | Myocardial infarction; Angina pectoris; Coronary vasospasm |
| Vascular disorders | | Slight increases in blood pressure; Transient increases in systemic blood pressure | | |
| Gastrointestinal disorders | Abdominal pain; Nausea; Vomiting; Dry mouth; Dysphagia | | | 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 | Muscle weakness; Myalgia | | | |

| System Organ Class | Common | Uncommon | Rare | Very rare |
|------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------|-------------|------------------|
| Renal and Urinary disorders | | Polyuria; Increased urinary frequency | | Urinary urgency |
| General disorders and administration site disorders | Asthenia; Heaviness, tightness, pain or pressure in throat, neck, limbs or chest | | | |

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system; to be completed nationally according to Appendix V of the QRD template].

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 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: Analgesics, Selective serotonin (5HT₁) agonists.
 ATC code: N02CC03

Mechanism of action

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 (5HT₂, 5HT₃, 5HT₄) or adrenergic, histaminic, muscarinic or dopaminergic receptors.

Pharmacodynamic effects

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).

Clinical efficacy and safety

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 should be taken during the headache phase of migraine.

Paediatric population

One controlled clinical trial in 696 adolescents with migraine failed to demonstrate superiority of zolmitriptan tablets at doses of 2.5 mg, 5 mg and 10 mg over placebo. Efficacy was not demonstrated.

5.2 Pharmacokinetic properties

Absorption

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%.

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 administration of the medicinal product 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 N-desmethylzolmitriptan. 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).

Distribution

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%).

Biotransformation

Metabolism of zolmitriptan is dependent on CYP1A2 and the metabolism of the active metabolite N-desmethylzolmitriptan is via the monoamine oxidase A (MAOA) enzyme system.

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. The N-desmethyl metabolite is also a 5HT_{1B/1D} receptor agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan. 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.

Elimination

Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. 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 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.

Special populations

Renal impairment

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.

Hepatic impairment

A study to evaluate the effect of hepatic impairment on the pharmacokinetics of zolmitriptan showed that the AUC and C_{max} were increased by 94% and 50% respectively in patients with moderate hepatic impairment and by 226% and 47% respectively in patients with severe hepatic impairment compared with healthy volunteers. Exposure to the metabolites, including the active metabolite, was decreased. For the active metabolite N-desmethylzolmitriptan, AUC and C_{max} were reduced by 33% and 44% respectively in patients with moderate hepatic impairment and by 82% and 90% respectively in patients with severe hepatic impairment.

Elderly

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

Silicified microcrystalline cellulose
Crospovidone
Sodium hydrogen carbonate
Anhydrous citric acid
Colloidal anhydrous silica
Mannitol (E 421)
Sweet orange flavour (contains sodium, sulphites and propylene glycol)
Aspartame (E 951)
Magnesium stearate

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

The orodispersible tablets are packed in Alu/Alu blisters and inserted in a carton.

[NL/H/1907/002]

Pack sizes: 2, 3, 4, 6, 10, 12, 18, 24 orodispersible tablets

[NL/H/1907/004]

Pack sizes: 2, 3, 4, 6, 12, 18, 24 orodispersible tablets

[NL/H/1908-1909/002-004]

Pack sizes: 2, 3, 6, 12, 18 orodispersible tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Veluwezoom 22
Almere
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 106564
RVG 106565

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 31 mei 2011
Datum van laatste hernieuwing: 23 december 2015

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.3, 4.5, 4.7 en 5.2: 18 augustus 2021