# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Zolmitriptan Sanofi 2.5mg orodispersible tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 2.5 mg of zolmitriptan.
Excipient with known effect: Each tablet contains also 2.5 mg of aspartame (E951).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Orodispersible tablet
White to off-white, round, flat faced beveled edge uncoated tablet of 6.4 ± 0.3 mm diameter and with '2.5' debossed on one side and plain on other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Zolmitriptan Sanofi is indicated for the acute treatment of migraine headache with or without aura.

Zolmitriptan Sanofi is not indicated for prophylaxis of migraine.

### 4.2 Posology and method of administration

Posology:
The recommended dose is 2.5 mg zolmitriptan. It is advisable that Zolmitriptan Sanofi 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 zolmitriptan, for subsequent attacks doses of 5 mg zolmitriptan could be considered.
The total daily intake should not exceed 10 mg. Not more than 2 doses should be taken in any 24 hour period.

Special populations:

*Patients aged over 65 years*
Safety and efficacy of Zolmitriptan Sanofi in patients aged over 65 years have not been established. Use of Zolmitriptan Sanofi in the elderly is therefore not recommended.

*Patients with hepatic impairment*
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 zolmitriptan in 24 hours is recommended. However, no dose adjustment is required for patients with mild hepatic impairment.

*Patients with renal impairment*
No dosage 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).

*Children (under 12 years of age)*
Safety and efficacy of zolmitriptan in children have not been evaluated. Use of Zolmitriptan Sanofi in children is therefore not recommended.

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

*Method of administration:*

The orodispersible tablet need not be taken with liquid; the orodispersible tablet rapidly dissolves when placed on the tongue and swallowed with the patient's saliva. The orodispersible tablet can be used in situations in which liquids are not available. Orodispersible tablets may also be beneficial for patients who suffer from nausea and are unable to drink during a migraine attack, or for patients who do not like swallowing conventional tablets. However, a delay in the absorption of zolmitriptan from orodispersible tablets can occur which may delay the 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.
- A history of myocardial infarction or ischaemic heart disease.
- Patients with symptoms or signs consistent with ischaemic heart disease.
- Coronary vasospasm/Prinzmetal's angina.
- Peripheral vascular disease.
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Concomitant administration of zolmitriptan with ergotamine or ergotamine derivatives (including methysergide) or other 5-$HT_{1B/1D}$ receptor agonists (e.g. sumatriptan, naratriptan).
- Creatinine clearance lower than 15 ml/min.

## 4.4 Special warnings and precautions for use

Zolmitriptan Sanofi 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 Sanofi is not indicated for use in hemiplegic, basilar or ophthalmophlegic migraine. Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with $5HT_{1B/1D}$ agonists. 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 5-$HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris and myocardial infarction have been reported. Zolmitriptan Sanofi 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 5-$HT_{1B/1D}$ 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 5-$HT_{1B/1D}$ 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.

As with other 5-$HT_{1B/1D}$ agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

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.

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. hyperreflexia, 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 is clinically warranted, particularly during treatment initiation and dosage increases (see section 4.5).

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

Zolmitriptan, when administered as conventional oral tablets, if taken during the aura, has not been demonstrated to prevent the migraine headache and therefore Zolmitriptan Sanofi should be taken during the headache phase of migraine.

Zolmitriptan Sanofi contains aspartame (E951). Aspartam contains a source of phenylalanine. May be harmful for people with phenylketonuria.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

Data from healthy subjects suggest 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. Therefore, 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 any ergotamine containing 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 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 (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 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).

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 (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see section 4.4).

As with other 5-$HT_{1B/1D}$ receptor agonists, zolmitriptan could delay the absorption of other medicinal products. Concomitant administration of other 5-$HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment should be avoided. Similarly, administration of zolmitriptan within 24 hours of the use of other 5-$HT_{1B/1D}$ agonists should be avoided.

As with other $5HT_{IB/ID}$ agonists, there is the potential for dynamic interactions with the herbal remedy St John's wort (Hypericum perforatum) which may result in an increase in undesirable effects.

## 4.6 Fertility, pregnancy and lactation

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

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

*Fertility*
There are no data indicating that zolmitriptan may affect fertility.

## 4.7 Effects on ability to drive and use machines

Zolmitriptan Sanofi has no or negligible influence on the ability to drive and use machines.
There was no significant impairment of performance of psychomotor tests with doses up to 20 mg zolmitriptan in a small group of healthy individuals. 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 adverse reactions are typically transient, tend to occur within 4 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 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).

| **System organ class** | **Frequency** | **Undesirable effects** |
|---|---|---|
| Immune system | Rare | Anaphylaxis/Anaphylactoid Reactions |

| | | |
|---|---|---|
| disorders | | Hypersensitivity reactions including urticaria, angioedema |
| Nervous system disorders | Common | Abnormalities or disturbances of sensation<br>Dizziness<br>Headache<br>Hyperaesthesia<br>Paraesthesia<br>Somnolence<br>Warm sensation |
| Cardiac disorders | Common | Palpitations |
| | Uncommon | Tachycardia |
| | Very rare | Angina pectoris<br>Coronary vasospasm<br>Myocardial infarction |
| Vascular disorders | Uncommon | Slight increases in blood pressure<br>Transient increases in systemic blood pressure |
| Gastrointestinal disorders | Common | Abdominal pain<br>Dry mouth<br>Nausea<br>Vomiting<br>Dysphagia |
| | Very rare | Gastrointestinal infarction or necrosis<br>Gastrointestinal ischaemic events which may present as bloody diarrhoea or abdominal pain<br>Ischaemic colitis<br>Splenic Infarction |
| Musculoskeletal and connective tissue disorders | Common | Muscle weakness<br>Myalgia |
| Renal and urinary disorders | Uncommon | Polyuria<br>Increased urinary frequency |
| | Very rare | Urinary urgency |
| General disorders and administration site conditions | Common | Asthenia<br>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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie  E-mail: medsafety@hpra.ie

## 4.9 Overdose

Volunteers receiving single oral doses of 50 mg commonly experienced sedation.

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 Sanofi 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 demonstrated to be a selective agonist for the vascular human recombinant 5-$HT_{1B}$ and 5-$HT_{1D}$ receptor subtypes. Zolmitriptan is a high affinity 5-$HT_{1B/1D}$ receptor agonist with modest affinity for 5-$HT_{1A}$ receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at other 5-HT receptors 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 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 Sanofi should be taken during the headache phase of migraine.

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

## 5.2 Pharmacokinetic properties

Following oral administration of zolmitriptan conventional tablets zolmitriptan is rapidly and well absorbed (at least 64%) after oral administration to man. The mean absolute bioavailability of the parent compound is approximately 40%. There is an active metabolite (183C91, the N-desmethyl metabolite) which is also a 5-$HT_{IB/1D}$ receptor agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan.

In healthy subjects, when given as a single dose, zolmitriptan and its active metabolite the N−desmethyl metabolite, display dose-proportional AUC and $C_{max}$ over the dose range 2.5 to 50 mg. Absorption of zolmitriptan is rapid in healthy volunteers, 75% of $C_{max}$ is achieved within 1 hour and after this the concentration of zolmitriptan in plasma is maintained at approximately this level until 4 to 5 hours after dosing. Zolmitriptan absorption is unaffected by the presence of food. There is 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. 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.

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 183C91 metabolite, 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.

The plasma half-life ($t_{½}$) of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate hepatic impairment and 12 hours in those with severe liver disease. The corresponding $t_{½}$ values for the 183C91 metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively.

Following intravenous administration, the mean total plasma clearance is approximately 10 ml/min/kg, of which one quarter is renal clearance. Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion. The volume of distribution following intravenous administration is 2.4 L/kg. Plasma protein binding of zolmitriptan and the N-desmethyl metabolite is low (approximately 25%). The mean elimination half-life of zolmitriptan is 2.5 to 3 hours. The half-lives of its metabolites are similar, suggesting their elimination is formation-rate limited.

Renal clearance of zolmitriptan and all its metabolites is reduced (7 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 pharmacokinetics of zolmitriptan in healthy elderly subjects was similar to those in healthy young volunteers.

Zolmitriptan orodispersible tablets were demonstrated to be bioequivalent with the conventional tablet in terms of AUC and $C_{max}$ for zolmitriptan and its active metabolite 183C91. Clinical pharmacology data show that the $t_{max}$ for zolmitriptan can be later for the orally dispersible tablet (range 0.6 to 5h, median 3h) compared to the conventional tablet (range 0.5 to 3h, median 1.5h). The $t_{max}$ for the active metabolite was similar for both formulations (median 3h).

## 5.3 Preclinical safety data

Preclinical effects in single and repeat dose toxicity studies were observed only at exposures well in excess of the maximum human exposure.

The findings from in vitro and in vivo genetic toxicity studies show that genotoxic effects of zolmitriptan are not to be expected under the conditions of clinical use.

No tumours relevant to the clinical use were found in mouse and rat carcinogenicity studies.

As with other $5HT_{1B/1D}$ receptor agonists, zolmitriptan binds to melanin.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Mannitol (E421)

Cellulose Microcrystalline
Aspartame (E951)
Croscarmellose sodium
Sillica Colloidal Anhydrous
Magnesium stearate (E470b)
Orange flavour (containing nature-identical flavouring substance(s), flavouring preparation, natural flavouring substance(s), maltodextrin (Maize), arabic gum (acacia gum) (E414), ascorbic acid (E300) and butylated hydroxyanisole (E320).

## 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 temperature storage conditions.
Store in the original inner package (blister) in order to protect from moisture.

## 6.5 Nature and contents of container

Zolmitriptan Sanofi orodispersible tablets are supplied in OPA/Al/PVC/Al blister.

Size of packing: 2 and 6 orodispersible tablets

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

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus,
Dublin 24,
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA0540/172/002

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th April 2014

## 10 DATE OF REVISION OF THE TEXT

January 2015