## 1. NAME OF THE MEDICINAL PRODUCT

Zolmitriptan Grünenthal 5 mg Nasal Spray.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zolmitriptan Grünenthal Nasal Spray is an aqueous solution containing 50 mg/ml zolmitriptan, buffered to pH 5.0. The device delivers a unit dose of 5 mg and is intended for a single use only.

For the full list of excipients, see Section 6.1.

## 2. 3 PHARMACEUTICAL FORM

Nasal Spray.

## 3. 4.1 THERAPEUTIC INDICATION

Zolmitriptan Grünenthal Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults and adolescents aged 12 years and older.

## 4. 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

The recommended dose of Zolmitriptan Grünenthal Nasal Spray to treat a migraine attack is 5 mg.

Zolmitriptan Grünenthal Nasal Spray is administered as a single dose into one nostril. Zolmitriptan Grünenthal Nasal Spray provides particularly rapid onset of relief of migraine with the first signs of efficacy apparent within 15 minutes of dosing.

Zolmitriptan Grünenthal Nasal Spray provides an alternative non–oral formulation of zolmitriptan to that of Zomig oral tablets and orodispersible tablets. This formulation may also be beneficial where a non–oral route of treatment is either needed or preferred.

If symptoms persist or return within 24 hours a second dose has been shown to be effective. If a second dose is required, it should not be taken within 2 hours of the initial dose.

Zolmitriptan Grünenthal Nasal Spray is effective whenever the nasal spray is administered during a migraine attack; although it is advisable that Zolmitriptan Grünenthal Nasal Spray is taken as early as possible after the onset of migraine headache.

In the event of recurrent attacks, it is recommended that the total intake of Zolmitriptan Grünenthal Nasal Spray in a 24 hour period should not exceed 10 mg.

Zolmitriptan Grünenthal Nasal Spray is not indicated for prophylaxis of migraine.

*Paediatric population (under 12 years of age)*
The safety and efficacy of Zolmitriptan Grünenthal Nasal Spray in children aged 12 years or under has not yet been established. Use of Zolmitriptan Grünenthal Nasal Spray in children is therefore not recommended.

*Use in adolescents (from the age of 12 years)*
The recommended dose of Zolmitriptan Grünenthal Nasal to treat a migraine attack is 5 mg. It is advisable that Zolmitriptan Grünenthal Nasal is taken as early as possible after the onset of migraine headache but it is also effective if taken at a later stage.

*Elderly*
The safety and efficacy of Zolmitriptan Grünenthal Nasal Spray in individuals aged over 65 years have not been systematically evaluated.

*Hepatic Impairment*
The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. However, for patients with moderate or severe hepatic impairment metabolism after oral dosing is reduced and a maximum dose of 5 mg oral zolmitriptan in 24 hours is recommended (see Section 5.2).

*Renal Impairment*
No dosage adjustment required (see Section 5.2).

Method of administration

For nasal inhalation.

## 4.3 Contraindications

Zolmitriptan Grünenthal Nasal Spray is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1
- Uncontrolled hypertension
- Ischaemic heart disease
- Coronary vasospasm/Prinzmetal's angina
- A history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA)
- Concomitant administration of Zolmitriptan Grünenthal Nasal Spray with ergotamine or ergotamine derivatives or other 5-$HT_1$ receptor agonists.

## 4.4 Special warnings and precautions for use

Zolmitriptan Grünenthal Nasal Spray should only be used where a clear diagnosis of migraine has been established. Care should be taken to exclude other potentially serious neurological conditions. There are no data on the use of Zolmitriptan Grünenthal Nasal Spray in hemiplegic or basilar migraine. Migraineurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with $5HT_{1B/1D}$ agonists.

Zolmitriptan Grünenthal Nasal Spray 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. In patients with risk factors for ischaemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including Zolmitriptan Grünenthal Nasal Spray, is recommended (see Section 4.3). 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 $5HT_{1B/1D}$ agonists, atypical sensations over the precordium (see Section 4.8) have been reported after the administration of Zolmitriptan Grünenthal Nasal Spray.

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.

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

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 serotonergic drugs, 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°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 dosage increases (see Section 4.5).

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

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

From studies using oral zolmitriptan tablets, there is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of Zolmitriptan Grünenthal Nasal Spray (for example beta-blockers, oral dihydroergotamine, pizotifen).

The pharmacokinetics and tolerability of Zomig oral tablets were unaffected by acute symptomatic treatments such as paracetamol, metoclopramide and ergotamine.

Concomitant administration of other $5HT_{1B/1D}$ agonists within 24 hours of Zolmitriptan Grünenthal Nasal Spray treatment should be avoided.

Data from healthy subjects suggest that there are no pharmacokinetic or clinically significant interactions between Zolmitriptan Grünenthal Nasal Spray and ergotamine, however, the increased risk of coronary vasospasm is a theoretical possibility. Therefore, it is advised to wait at least 24 hours following the use of ergotamine containing preparations before administering Zolmitriptan Grünenthal Nasal Spray. Conversely, it is advised to wait at least six hours following use of Zolmitriptan Grünenthal Nasal Spray before administering any ergotamine preparation (see Section 4.3).

Following co-administration of moclobemide, a specific MAO-A inhibitor, and Zomig oral tablets, 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 Grünenthal Nasal Spray in 24 hours is recommended in patients taking an MAO-A inhibitor.

Following the co-administration of cimetidine, a general P450 inhibitor, and Zomig oral tablets, 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 metabolite (N-desmethylzolmitriptan) were doubled. A maximum dose of 5 mg Zolmitriptan Grünenthal Nasal Spray 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).

Fluoxetine did not affect the pharmacokinetic parameters of zolmitriptan in a study using oral zolmitriptan tablets. Therapeutic doses of the specific serotonin reuptake inhibitors, fluoxetine, sertraline, paroxetine and citalopram do not inhibit CYP1A2. However, Serotonin Syndrome has been reported during combined use of triptans, and SSRIs (e.g. fluoxetine, paroxetine, sertraline) and SNRIs (e.g. venlafaxine, duloxetine) (see section 4.4).

As with other $5HT_{1b/1d}$ 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.

The absorption and pharmacokinetics of Zolmitriptan is unaltered by prior administration of the sympathomimetic vasoconstrictor, xylometazoline.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Zolmitriptan Grünenthal Nasal Spray should be used in pregnancy only if the benefits to the mother justify potential risk to the foetus. There are no studies in pregnant women, but there is no evidence of teratogenicity in animal studies (see Section 5.3).

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 Grünenthal Nasal Spray to women who are breast-feeding.

## 4.7 Effects on ability to drive and use machines

There was no significant impairment of performance of psychomotor tests with doses up to 20 mg oral Zomig. Zolmitriptan Grünenthal Nasal Spray has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that somnolence may occur.

# 5. 4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Zolmitriptan is well tolerated. Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment.

Possible adverse reactions tend to occur within 4 hours of dosing and are no more frequent following repeated dosing.

Tabulated list of adverse reactions

Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: 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). The following undesirable effects have been reported following administration with zolmitriptan:

| **System Organ Class** | **Frequency** | **Undesirable Effect** |
|---|---|---|
| Immune system disorders | Rare | Anaphylaxis/Anaphylactoid Reactions;<br>Hypersensitivity reactions. |
| Nervous system disorder | Very common | Taste disturbance. |
| | 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 | Transient increases in systemic blood;pressure. |
| Respiratory , thoracic and mediastinal disorders | Common | Epistaxis;<br>Discomfort of nasal cavity. |

| | | |
|---|---|---|
| Gastrointestinal disorders | Common | Abdominal pain;<br>Dry mouth;<br>Nausea;<br>Vomiting;<br>Dysphagia. |
| | Very rare | Bloody diarrhoea;<br>Gastrointestinal infarction or necrosis;<br>Gastrointestinal ischaemic events;<br>Ischaemic colitis;<br>Splenic infarction. |
| Skin and subcutaneous tissue disorders | Rare | Angioedema;<br>Urticaria. |
| 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. |

Paediatric population

Data from multicentre, double-blind, randomised placebo-controlled, cross-over clinical trial involving 168 paediatric subjects (6 to 11 years) with migraine headache as well as post-marketing data support the adverse event profile. The type and severity of adverse reactions were similar to those in adults. However, no statements can be made regarding the frequencies. No new safety issues have been identified from the completed paediatric trial for the age group investigated.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Symptoms

There has been no experience of overdose with zolmitriptan nasal spray.
Volunteers receiving single oral doses of 50 mg commonly experienced sedation.

Management
The elimination half-life of zolmitriptan following intranasal administration is 3 hours, (see Section 5.2) and therefore monitoring of patients after overdose with Zolmitriptan Grünenthal Nasal Spray 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.

# 6. 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Selective serotonin ($5HT_1$) agonists. ATC code: N02CC03

Mechanism of action
In pre-clinical studies, zolmitriptan has been demonstrated to be a selective agonist for the vascular human recombinant $5HT_{1B}$ and $5HT_{1D}$ receptor subtypes. Zolmitriptan is a high affinity $5HT_{1B/1D}$ receptor agonist with modest affinity for $5HT_{1A}$ receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at $5HT_2$-, $5HT_3$-, $5HT_4$-, $alpha_1$-, $alpha_2$-, or $beta_1$-, adrenergic; $H_1$-, $H_2$-, histaminic; muscarinic; $dopaminergic_1$, or $dopaminergic_2$ receptors.

The $5HT_{1B/1D}$ receptor is predominantly located presynaptically at both the peripheral and central synapses of the trigeminal nerve and preclinical studies have shown that zolmitriptan is able to act at both these sites.

Clinical efficacy and safety
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.

*Adolescent migraine patients*

A multicentre, double-blind, randomised placebo-controlled, 2-way cross-over study was conducted to evaluate the efficacy of zolmitriptan 5 mg nasal spray in the acute treatment of migraine headache. The study included a single-blind, placebo challenge for each of two attacks and included 171 evaluable adolescent subjects aged 12 to 17 years. The results for the primary endpoints of one hour headache response (defined as an improvement in migraine headache intensity from severe or moderate to mild or none) and two hour sustained headache response were 58.1% vs. 43.3% ($p=0.013$) and 51.4% vs. 33.1% ($p=0.003$) for zolmitriptan vs. placebo, respectively. In addition, 27.7% and 39.2% of zolmitriptan treated patients were pain free at one and two hours respectively vs. 10.2% and 18.9% of placebo patients ($p<0.001$).

A multicentre, double-blind, randomised, placebo-controlled, 4-armed parallel group study evaluated the efficacy of zolmitriptan 2.5- and 5-mg nasal spray in the treatment

of acute migraine headache in adolescents (n=798). This study demonstrated the superiority of Zolmitriptan 5 mg nasal spray to placebo in reducing the pain associated with adolescent migraines. Zolmitriptan 5 mg achieved the primary efficacy endpoint of pain-free status at two hours after treatment. Secondary analyses addressing extent and durability of pain mitigation, use of rescue medication, and ability to return to normal activities support the therapeutic benefit of Zolmitriptan 5 mg.

## 7. 5.2 PHARMACOKINETIC PROPERTIES

Zolmitriptan, following intranasal administration, is rapidly absorbed with detectable levels in the plasma within 5 minutes of dosing. A proportion of the dose seems to be directly absorbed in the naso-pharynx. On average 40% of $C_{max}$ of the parent compound, zolmitriptan, is achieved within 15 minutes. The appearance in plasma of the active metabolite, N-desmethylzolmitriptan, which is partly formed through first-pass metabolism, is delayed by 15 to 60 minutes post-dose. $C_{max}$ of the parent compound, zolmitriptan is achieved after 3 hours. Plasma concentrations are sustained for up to 4 to 6 hours. Elimination of zolmitriptan and the active metabolite N-desmethylzolmitriptan after oral and intranasal delivery appear similar; the mean elimination half-life (t½) for both zolmitriptan and N-desmethylzolmitriptan are approximately 3 hours. The bioavailability of intranasal relative to oral administration is 102%. In healthy volunteers after single and multiple intranasal doses, zolmitriptan and its active metabolite N-desmethylzolmitriptan display dose proportional AUC and $C_{max}$ over the range 1 to 5 mg. There is no evidence of accumulation of zolmitriptan after multiple intranasal dosing.

The plasma concentrations and elimination pharmacokinetics of zolmitriptan and the three major metabolites for the nasal spray and conventional tablet formulations are similar.

Following oral administration of Zomig conventional tablets, zolmitriptan is rapidly and well absorbed (at least 64%). The mean absolute bioavailability of the parent compound is approximately 40%.

Absorption is rapid with 75% of $C_{max}$ achieved within 1 hour and plasma concentrations are sustained subsequently for 4 to 6 hours. After oral administration zolmitriptan absorption is unaffected by the presence of food.

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-desmethyl metabolite ) is an active metabolite which is also a 5H $_{1B/1D}$ agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan. 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. Plasma concentrations of N-desmethyzolmitriptan 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 using oral zolmitriptan to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and $C_{max}$ 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. Exposure to the metabolites, including the active metabolite, was decreased. For the N-desmethylzolmitriptan metabolite, AUC and $C_{max}$ were reduced by 33% and 44% in patients with moderate liver disease and by 82% and 90% in patients with severe liver disease.

The plasma half-life ($T_{½}$) of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding $T_{½}$ values for the N-desmethylzolmitriptan metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively. No studies have been undertaken to characterise the pharmacokinetics of intranasally administered zolmitriptan in patients with hepatic impairment.

Following intravenous administration, the mean total plasma clearance is approximately 10 ml/min/kg, of which one third 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. These findings originate from studies with zolmitriptan tablets.

In a small group of healthy individuals there was no pharmacokinetic interaction with ergotamine. Concomitant administration of Zolmitriptan with ergotamine/caffeine was well tolerated and did not result in any increase in adverse events or blood pressure changes as compared with Zolmitriptan alone (see Section 4.5). These findings originate from studies with zolmitriptan tablets.

Selegiline, an MAO-B inhibitor, and fluoxetine (a selective serotonin reuptake inhibitor; SSRI) had no effect on the pharmacokinetic parameters of zolmitriptan (see Section 4.4). These findings originate from studies with zolmitriptan tablets.

Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed. The findings originate from studies with zolmitriptan tablets.

The pharmacokinetics of zolmitriptan in healthy elderly subjects were similar to those in healthy young volunteers. These findings originate from studies with zolmitriptan tablets.

The absorption of zolmitriptan nasal spray in healthy volunteers was found unaltered when administered concomitantly with the sympathomimetic nasal decongestant, xylometazoline.

*Paediatric population*

Pharmacokinetic results were similar in adolescents and adults. The exposure of zolmitriptan is similar to slightly reduced in adolescents as compared to adults. Correspondingly, the exposure of the active metabolite is somewhat increased. The differences lack clinical significance.

## 5.3 Preclinical safety data

An oral teratology study of Zolmitriptan has been conducted. At the maximum tolerated doses of Zomig, 1200 mg/kg/day (AUC 605 µg/ml.h : approx. 3700 x AUC of the human maximum recommended daily intake of 15 mg) and 30 mg/kg/day (AUC 4.9 µg/ml.h : approx. 30 x AUC of the human maximum recommended daily intake of 15 mg) in rats and rabbits, respectively, no signs of teratogenicity were apparent.

A number of genotoxicity tests have been performed. It was concluded that Zomig is not likely to pose any genetic risk in humans.

Carcinogenicity studies in rats and mice were conducted at the highest feasible doses and gave no suggestion of tumorogenicity.

Reproductive studies in male and female rats, at dose levels limited by toxicity, revealed no effect on fertility.

## 6.1 List of excipients

Each Zolmitriptan Grünenthal Nasal Spray vial contains the following excipients:

Citric acid
Disodium phosphate
Purified Water

## 7.1 6.2 Incompatibilities

Not applicable.

## 7.2 6.3 Shelf life

30 months

## 7.3 6.4 Special precautions for storage

Do not store above 25$^{o}$C.

## 7.4 6.5 Nature and contents of container

Ph Eur Type I glass vials which are closed with chlorobutyl rubber stoppers. The vials are assembled into a unit dose nasal spray device, comprising of a vial holder, an actuation device and a protection cover.

Packs containing 1, 2, or 6 single use devices.

Not all pack sizes may be marketed.

## 7.5 6.6 Special precautions for disposal

The protection cover must not be removed until immediately before use. For instructions for use see the patient information leaflet.

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

## 8. 7 MARKETING AUTHORISATION HOLDER

Grünenthal Limited

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United Kingdom

## 9. 8 MARKETING AUTHORISATION NUMBER(S)

PL 21727/0085

## 10. 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 September 2002

## 10 DATE OF REVISION OF THE TEXT

15/01/2026