SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zomig Nasal 5 mg/dose, nasal spray, solution
Zomig Nasal 2.5 mg/dose, nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zomig Nasal 5 mg/dose nasal spray contains zolmitriptan 50 mg/ml corresponding to 5 mg zolmitriptan per dose.
Zomig Nasal 2.5 mg/dose nasal spray contains zolmitriptan 25 mg/ml corresponding to 2.5 mg zolmitriptan per dose.

The solution is buffered to pH 5.0.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution.

A clear, colourless to yellow liquid. In glass vials in a single unit dose nasal spray device.

The device is intended for a single use only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zomig Nasal is indicated in adults and adolescents aged 12 years and older for the acute treatment of migraine headache with or without aura and in adults for the acute treatment of cluster headache.

4.2 Posology and method of administration

Posology

Treatment of migraine

Adults

The recommended dose of Zomig Nasal to treat a migraine attack is 2.5 mg or 5 mg. For those patients that do not achieve satisfactory effect with 2.5 mg a dose of 5 mg may be effective at subsequent attacks. It is advisable that Zomig Nasal is taken as early as possible after the onset of migraine headache but it is also effective if taken at a later stage.

Adolescents (from the age of 12 years)

The recommended dose of Zomig Nasal to treat a migraine attack is 2.5 mg or 5 mg. For those patients that do not achieve satisfactory effect with 2.5 mg, a dose of 5 mg may be effective at subsequent

attacks. It is advisable that Zomig Nasal 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. The total daily intake must not exceed 10 mg, therefore, not more than 2 doses of zolmitriptan 5 mg should be taken in any 24-hour period.

For adult patients Zomig Nasal provides an alternative to that of Zomig tablets and may be especially beneficial in patients suffering from nausea and vomiting during the migraine attack. However, it should be noted that identical doses of Zomig tablet and Zomig Nasal may not provide identical efficacy (see section 5.1).

Treatment of cluster headache

The recommended dose of Zomig Nasal to treat a cluster headache attack is 5 or 10 mg. For those patients that do not achieve satisfactory effect with 5 mg a dose of 10 mg may be effective at subsequent attacks. It is advisable that Zomig Nasal is taken as early as possible after the onset of cluster headache.

The total daily intake must not exceed 10 mg, therefore, not more than 4 doses of zolmitriptan 2.5 mg or 2 doses of zolmitriptan 5 mg should be taken, in any 24-hour period.

Zomig Nasal is not indicated for prophylaxis of migraine or cluster headache.

Paediatric population

Use in children (under 12 years of age)

The efficacy of Zomig Nasal in children aged 6 to < 12 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.
No data are available in children below 6 years. Use of Zomig Nasal in children < 12 years is therefore not recommended.

Special populations

Use in patients over 65 years

Safety and efficacy of Zomig Nasal in individuals aged over 65 years have not been established. Use of Zomig Nasal 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 dosage adjustment required in patients with a creatinine clearance of more than 15 ml/min (see section 4.3 and section 5.2).

Dosing recommendations for interactions (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 Zomig Nasal in 24 hours is recommended in patients taking cimetidine.

A maximum dose of 5 mg Zomig Nasal 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

Treatment of migraine

Zomig Nasal is administered as a single dose into one nostril.

Treatment of cluster headache

Cluster headache patients may experience a blocked nostril on the same side as their pain. In such cases it is recommended that Zomig Nasal is administered in the nostril contralateral to the pain.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Moderate and 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, or ergotamine derivatives (including methysergide), 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 or cluster headache has been established. As with other acute headache therapies, before treating patients not previously diagnosed as migraineurs or cluster headache sufferers, and in patients 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 patients 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. For patients with risk factors for ischaemic heart disease (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus, heredity) a prior cardiovascular evaluation should be made before treatment with zolmitriptan is initiated (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 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 ZOMIG 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Data from healthy subjects suggests there are no 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).

Pharmacokinetic interactions (effects of zolmitriptan on the pharmacokinetics of other medicinal products)

Following administration of moclobemide, 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.

Treatment with potent CYP1A2 inhibitors may increase the plasma concentrations of zolmitriptan and reduce the concentrations of the active metabolite. The clinical relevance of this is unknown. Dosage 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.

Pharmacokinetic interactions (effects of other medicinal products on the pharmacokinetics of zolmitriptan)

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.

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

Interaction studies have only been performed in adults. However, there is no indication of a different interaction profile among adolescents.

4.6 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.

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

Zomig 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 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 (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects have been reported following administration with zolmitriptan:

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Hypersensitivity reactions including urticaria, angioedema and anaphylactic reactions
Nervous system disorders	Very common	Taste disturbances
	Common	Abnormalities or disturbances or 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
Respiratory, thoracic and mediastinal disorders	Common	Nose bleed; Discomfort of nasal cavity; Non-infectious rhinitis
Gastrointestinal disorders	Common	Abdominal pain; Nausea; Vomiting; Dry mouth Dysphagia
	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	Common	Asthenia;

System Organ Class	Frequency	Undesirable Effect
administration site disorders		Heaviness, tightness, pain or pressure in throat, neck, limbs or chest.

The incidence of local adverse events was dose related.

Certain symptoms may be part of the migraine attack itself.

Frequency, type and severity of adverse events are similar in adults and adolescents.

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 national reporting system listed in Appendix V

4.9 Overdose

Volunteers receiving single oral doses of 50 mg zolmitriptan 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 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: Selective serotonin ($5HT_1$) agonists, ATC code: N02CC03

Mechanism of action

Zolmitriptan has been demonstrated to be a selective agonist for 5-$HT_{1B/1D}$ receptors mediating vascular contraction. Zolmitriptan has a high affinity for human recombinant 5-HT_{1B} and 5-HT_{1D} receptors, with modest affinity for 5-HT_{1A} receptors. Zolmitriptan has no significant affinity or pharmacological activity at other 5-HT receptor subtypes (5-HT_2, 5-HT_3, $5HT_4$-) or adrenergic; histaminic; muscarinic; 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 the proportion of patients with undesirable effects has been shown to increase with increasing dose (see section 4.8).

Acute treatment of migraine

In a clinical trial with Zomig Nasal including just over 1300 migraine patients treating up to 3 migraine attacks, the dose 2.5 mg, 2 hours after administration, resulted in a reduction of headache from severe/moderate to mild/none in 59% of the attacks, while pain free was achieved in 26% of the attacks. Corresponding results for the 5 mg dose were 70% and 36% respectively and for placebo 31% and 8% respectively. After administration of both doses a statistically significant initial effect on headache was seen after 15 minutes (in 8% and 11% of the attacks for Zomig Nasal 2.5 and 5 mg respectively compared with 5% of the attacks for placebo). Due to the different pharmacokinetic profiles of the oral and nasal formulations, patients treated with 2.5 mg nasal spray may not achieve sufficient efficacy at later timepoints when compared with the 2.5 mg tablet.

Zomig, when administered as the conventional tablets, is consistently effective in migraine with or without aura and in menstrually associated migraine. Zomig, when administered as the conventional tablets, if taken during the aura, has not been demonstrated to prevent the migraine headache and therefore Zomig Nasal should be taken during the headache phase of the migraine.

Adolescent migraine patients

A multicenter, double-blind, randomized 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 ($p<0.001$).

Paediatric migraine patients

A multicentre, double-blind, randomised placebo-controlled, 2-way cross-over study with an open label extension was conducted to evaluate the efficacy of zolmitriptan 5 mg, 2.5 mg or 1 mg nasal spray in the acute treatment of migraine headache. The study included a single-blind, placebo challenge for one attack and included 168 evaluable subjects aged 6 to 11 years. The primary endpoint was not met and the clinical efficacy in this patient group was not established.

Acute treatment of cluster headache

Two controlled clinical trials with comparable design had a combined total of 121 patients, each treating up to 3 cluster headache attacks. In a pooled analysis of these two trials, Zomig Nasal 5 mg, 30 minutes after administration, resulted in a statistically significant reduction of headache from very severe/severe/moderate to mild/none in 48.3% of the patients versus 29.5% on placebo. Pain free was achieved in 34.8% of the patients versus 19.3% on placebo. Corresponding results for the 10 mg dose were 63.1% and 44.0% for headache response and pain free, respectively.

5.2 Pharmacokinetic properties

Absorption

Following intranasal administration, a proportion of the dose appears to be directly absorbed in the nasopharynx. The individual pharmacokinetic profile of zolmitriptan after nasal spray administration typically displays two peaks 0.5 to 5 hours after administration. Median T_{max} is around 2 hours. At 15 minutes after administration of zolmitriptan nasal spray to healthy volunteers on average 40% of C_{max} is achieved.
For the active metabolite, N-desmethylzolmitriptan median T_{max} is slightly later (around 3 hours after 2.5 mg and around 5 hours after 5 mg). Plasma concentrations of zolmitriptan and the metabolite N-desmethylzolmitriptan are sustained for up to 6 hours, with the average concentration at 6 hours being approximately 40% of C_{max} for zolmitriptan and 60% of C_{max} for N-desmethylzolmitriptan. Comparison of AUC after 2.5 mg intranasally (22.4 ng · hr/ml) relative to corresponding value after 2.5 mg orally (22.0 ng · hr/ml) showed that the bioavailability of intranasal zolmitriptan relative to oral administration is 102%.

Following oral administration, zolmitriptan is rapidly and well absorbed (at least 64%). The mean absolute bioavailability of the parent compound is approximately 40%. Zolmitriptan absorption is unaffected by the presence of food. There was no evidence of accumulation on multiple dosing of zolmitriptan when given orally.

After oral administration plasma concentrations 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.

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

Distribution

The volume of distribution following iv administration is 2.4 l/kg. Plasma protein binding of zolmitriptan and the N-desmethylated metabolite is approximately 25%.

Biotransformation
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 pharmacologically active whilst the others are not. Zolmitriptan is metabolised by CYP1A2, forming N-desmethylzolmitriptan, which is also a $5HT_{1B/1D}$ agonist and is 2 to 6 times as potent, in animal models, as zolmitriptan. The active metabolite is then further metabolised through MAO-A. 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.

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 indoleacetic 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 fourth is renal clearance. Renal clearance is greater than glomerular filtration rate suggesting renal tubular secretion.

Elimination of zolmitriptan and the active metabolite N-desmethylzolmitriptan after oral and intranasal delivery appears similar; the mean elimination half-life ($t_{½}$) for zolmitriptan is approximately 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 to 8 fold compared to healthy volunteers) in patients with moderate to severe renal impairment, 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.

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 probably lack clinical significance.

5.3 Preclinical safety data

Effects in single and repeat dose studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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

Citric acid, anhydrous
Disodium phosphate (dihydrate or dodecadihydrate)
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2.5 mg/dose nasal spray: 2 years.
5 mg/dose nasal spray: 30 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Ph Eur Type I glass vials with chlorobutyl rubber stoppers and spray device.

2.5 mg/dose nasal spray: unit dose spray device containing 0.1 ml solution.
Pack contains 1, 2 or 6 single use nasal spray units.

5 mg/dose nasal spray: unit dose spray device containing 0.1 ml solution.
Pack contains 1, 2, 6 or 18 single use nasal spray units.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]23 June 2023