Zolmitriptan Nasal Spray

1. Name of the medicinal product

Zolmitriptan Nasal Spray

2. Qualitative and quantitative composition

Zolmitriptan Nasal Spray is an aqueous solution containing 25 mg/mL zolmitriptan. The device delivers 2.5 mg of zolmitriptan per spray.

For the full list of excipients, see Section 6.1.

3. Pharmaceutical form

Nasal Spray

4. Clinical particulars

4.1 Therapeutic indications

Zolmitriptan Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults. Zolmitriptan Nasal Spray is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zolmitriptan Nasal Spray have not been established for cluster headache.

4.2 Posology and method of administration

The recommended starting dose for Zolmitriptan nasal spray is 2.5 mg. If the migraine has not resolved by 2 hours after taking Zolmitriptan nasal spray, or returns after a transient improvement, another dose may be administered at least 2 hours after the previous dose. The maximum daily dose should not exceed 10 mg in any 24-hour period.

Steps for using Zolmitriptan nasal spray:

Step 1: Blow your nose gently to clear your nasal passages before use.

Step 2: Remove the protective cap.

Step 3: When first time used, continuously press the sprayer to drain the gas in it until it sprayed out homogenously.

Step 4: Gently close 1 nostril with your index finger and insert the tip of the sprayer device into your open nostril about 1 cm, avoid contact with the nasal mucosa, tilt your head slightly, press the sprayer quickly to release the drug into your nasal.

4.3 Contraindications

Zolmitriptan nasal spray is contraindicated in patients with:

- Ischemic coronary artery disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), other significant underlying cardiovascular disease, or coronary artery vasospasm including Prinzmetal's angina.

- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

- History of stroke, transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at higher risk of stroke.

- Peripheral vascular disease (PVD).
- Ischemic bowel disease.
- Uncontrolled hypertension.
- Recent use (i.e., within 24 hours) of another 5-HT1 agonist, ergotamine-containing medication, or ergot-type medication (such as dihydroergotamine or methysergide).
- Concurrent administration of an MAO-A inhibitor or recent discontinuation of a MAO-A inhibitor (that is within 2 weeks).
- Known hypersensitivity to Zolmitripta nasal spray (angioedema and anaphylaxis seen).

4.4 Special warnings and precautions for use

Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

Zolmitriptan nasal spray is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD). There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of Zolmitriptan nasal spray. Some of these reactions occurred in patients without known CAD. 5-HT1 agonists including Zolmitriptan nasal spray may cause coronary artery vasospasm (Prinzmetal's Angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving Zolmitriptan nasal spray. Do not administer Zolmitriptan nasal spray if there is evidence of CAD or coronary artery vasospasm. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administrating the first Zolmitriptan nasal spray dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following Zolmitriptan nasal spray administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of Zolmitriptan nasal spray.

Arrhythmias

Life-threatening disturbances of cardiac rhythm including ventricular tachycardia and ventricular fibrillation leading to death have been reported within a few hours following the administration of 5-HT1 agonists. Discontinue Zolmitriptan nasal spray if these disturbances occur. Patients with Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive Zolmitriptan nasal spray.

Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure

As with other 5-HT1 agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with ZOMIG and is usually non-cardiac in origin. However, if a cardiac origin is suspected, patients should be evaluated. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT1 agonists.

Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT$_1$ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT$_1$ agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Discontinue Zolmitriptan nasal spray if a cerebrovascular event occurs.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with symptoms atypical for migraine, other potentially serious neurological conditions should be excluded. Zolmitriptan nasal spray should not be administered to patients with a history of stroke or transient ischemic attack.

Other Vasospasm Reactions

5-HT$_1$ agonists, including Zolmitriptan nasal spray, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of vasospasm reaction following the use of any 5-HT$_1$ agonist, the suspected vasospasm reaction should be ruled out before receiving additional Zolmitriptan nasal spray doses.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT$_1$ agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT$_1$ agonists have not been clearly established.

Medication Overuse Headache

Overuse of acute migraine drugs (e.g. ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Serotonin Syndrome

Serotonin syndrome may occur with triptans, including Zolmitriptan nasal spray, particularly during coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually rapidly occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Zolmitriptan nasal spray treatment should be discontinued if serotonin syndrome is suspected.

Increase in Blood Pressure

Significant elevations in systemic blood pressure have been reported in patients treated with 5-HT$_1$ agonists including patients without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. In healthy subjects treated with 5 mg of Zolmitriptan nasal spray oral tablet, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen. In a study of patients with moderate to severe liver impairment, 7 of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of Zolmitriptan nasal spray oral tablet. As with all triptans, blood pressure should be monitored in Zolmitriptan nasal spray-treated patients. Zolmitriptan nasal spray is contraindicated in patients with uncontrolled hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Ergot-containing drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and Zolmitriptan nasal spray within 24 hours of each other is contraindicated.

MAO-A Inhibitors

MAO-A inhibitors increase the systemic exposure of zolmitriptan. Therefore, the use of Zolmitriptan nasal spray in patients receiving MAO-A inhibitors is contraindicated.

5-HT1B/1D agonists (e.g. triptans)

Concomitant use of other 5-HT$_{1B/1D}$ agonists (including triptans) within 24 hours of Zolmitriptan nasal spray treatment is contraindicated because the risk of vasospastic reactions may be additive.

Cimetidine

Following administration of cimetidine, the half-life and AUC of Zolmitriptan nasal spray and its active metabolites were approximately doubled. If cimetidine and Zolmitriptan nasal spray are used concomitantly, limit the maximum single dose of Zolmitriptan nasal spray to 2.5 mg, not to exceed 5 mg in any 24-hour period.

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

It is not known whether zolmitriptan is excreted in human milk. Because many drugs are

excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Zolmitriptan nasal spray, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In rats, oral dosing with zolmitriptan resulted in levels in milk up to 4 times higher than in plasma.

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 Zolmitriptan. Zolmitriptan 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.

4.8 Undesirable effects

The following adverse reactions are discussed in more detail in other sections of labeling:

● Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina *[see Warnings and Precautions]*

● Arrhythmias *[see Warnings and Precautions]*

● Chest and or Throat, Neck and Jaw Pain/Tightness/Pressure *[see Warnings and Precautions]*

● Cerebrovascular Events *[see Warnings and Precautions]*

● Other Vasospasm Reactions *[see Warnings and Precautions]*

● Medication Overuse Headache *[see Warnings and Precautions]*

● Serotonin Syndrome *[see Warnings and Precautions]*

● Increase in Blood Pressure *[see Warnings and Precautions]*

4.9 Overdose

There is no experience with acute overdose. Clinical study subjects receiving single 50 mg oral doses of zolmitriptan commonly experienced sedation.

The elimination half-life of Zolmitriptan nasal spray is 3 hours and therefore monitoring of patients after overdose with Zolmitriptan 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.

It is unknown what effect hemodialysis or peritoneal dialysis has on the plasma concentrations of zolmitriptan.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors,

and moderate affinity for 5-HT_{1A} receptors. The N-desmethyl metabolite also has high affinity for 5-$HT_{1B/1D}$ and moderate affinity for 5-HT_{1A} receptors.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of Zolmitriptan nasal spray for the treatment of migraine headache is thought to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

5.2 Pharmacokinetic properties

Absorption:

Zolmitriptan nasal spray is rapidly absorbed via the nasopharynx as detected in a Photon Emission Tomography (PET) study using ^{11}C zolmitriptan. The mean relative bioavailability of the nasal spray formulation is 102%, compared with the oral tablet. Zolmitriptan was detected in plasma by 5 minutes and peak plasma concentration generally was achieved by 3 hours. The time at which maximum plasma concentrations were observed was similar after single (1 day) or multiple (4 days) nasal dosing. Plasma concentrations of zolmitriptan are sustained for 4 to 6 hours after dosing. Zolmitriptan and its active N-desmethyl metabolite display linear kinetics after single or multiple doses of Zolmitriptan nasal spray over the dose range of 0.1 to 10 mg.

The pharmacokinetics of the N-desmethyl metabolite are similar to that of zolmitriptan for all nasal spray dosages. The N-desmethyl metabolite is detected in plasma by 15 minutes and peak plasma concentration is generally achieved by 3 hours after administration.

Food has no significant effect on the bioavailability of zolmitriptan.

Distribution:

Plasma protein binding of zolmitriptan is 25% over the concentration range of 10-1000 ng/mL. The mean apparent volume of distribution for zolmitriptan nasal spray formulation is 8.4 L/kg.

Metabolism:

Zolmitriptan is converted to an active N-desmethyl metabolite such that the metabolite concentrations are about two-thirds that of zolmitriptan. Because the 5HT1B/1D potency of the metabolite is 2 to 6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after Zolmitriptan nasal spray administration.

Excretion:

The mean elimination half-life for zolmitriptan and N-desmethyl metabolite following single or multiple nasal spray administration are approximately 3 hours, similar to the half-life values seen after oral tablet administration.

In a study with orally administered zolmitriptan, total radioactivity recovered in urine and

feces was 65% and 30% of the administered dose, respectively. In urine, unchanged zolmitriptan and N-desmethyl metabolite accounted for 8% and 4% of the dose, respectively, whereas the inactive indole acetic acid and N-oxide metabolites accounted for 31% and 7% of the dose, respectively.

Mean total plasma clearance for zolmitriptan nasal spray is 25.9 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

5.3 Preclinical safety data

Carcinogenesis:

Zolmitriptan was administered to mice and rats at doses up to 400 mg/kg/day. Mice were dosed for 85 weeks (males) and 92 weeks (females); rats were dosed for 101 weeks (males) and 86 weeks (females). There was no evidence of drug-induced tumors in mice at plasma exposures (AUC) up to approximately 700 times that in humans at the maximum recommended human dose (MRHD) of 10 mg/day. In rats, there was an increase in the incidence of thyroid follicular cell hyperplasia and thyroid follicular cell adenomas in male rats receiving 400 mg/kg/day. No increase in tumors was observed in rats at 100 mg/kg/day, a dose associated with a plasma AUC ≈700 times that in humans at the MRHD.

Mutagenesis:

Zolmitriptan was positive in an *in vitro* bacterial reverse mutation (Ames) assay and in an *in vitro* chromosomal aberration assay in human lymphocytes. Zolmitriptan was negative in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay and in oral *in vivo* micronucleus assays in mouse and rat.

Impairment of Fertility:

Studies of male and female rats administered zolmitriptan prior to and during mating and up to implantation showed no impairment of fertility at oral doses up to 400 mg/kg/day. The plasma exposure (AUC) at this dose was approximately 3000 times that in humans at the MRHD.

6. Pharmaceutical particulars

6.1 List of excipients

Citric acid monohydrate

Disodium hydrogen phosphate

Benzalkonium chloride

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Protect from light. Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Packed in brown glass bottle, 15 sprays/bottle.

6.6 Special precautions for disposal and other handling

None.

Manufacturer

Name: Jewim Pharmaceutical (Shandong) Co. Ltd.
Address: Taian Hi-Tech Industrial Development Zone, Shandong, China.
Postcode: 271000
Tel: (0538) 8926688
Fax: (0538) 8926066
Website: www.jewimpharma.com