ZOLMIST Nasal Spray (Zolmitriptan)

Composition

Each ZOLMIST nasal spray dose unit supplies 5 mg of zolmitriptan.

Dosage Form

Nasal spray

Pharmacology

Pharmacodynamics

Zolmitriptan binds with high affinity to human recombinant 5-HT\textsubscript{1D} and 5-HT\textsubscript{1B} receptors. Zolmitriptan exhibits modest affinity for 5-HT\textsubscript{1A} receptors, but has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT\textsubscript{2}, 5-HT\textsubscript{3}, 5-HT\textsubscript{4}, alpha\textsubscript{1}, alpha\textsubscript{2}-adrenergic; H\textsubscript{1}, H\textsubscript{2}, histaminic; muscarinic; dopamine\textsubscript{1}, or dopamine\textsubscript{2} receptors. The N-desmethyl metabolite also has high affinity for 5-HT\textsubscript{1B/1D} and modest affinity for 5-HT\textsubscript{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 for the treatment of migraine headache can most likely be attributed to the agonist effects at the 5-HT\textsubscript{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.

Pharmacokinetics

Absorption

Zolmitriptan nasal spray is rapidly absorbed via the nasopharynx as detected in a Photon Emission Tomography (PET) study using \textsuperscript{11}C zolmitriptan. 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 day) nasal dosing. Plasma concentrations of zolmitriptan are sustained for 4 to 6 hours after dosing. Zolmitriptan displays linear kinetics after multiple doses of 2.5 mg, 5 mg, or 10 mg. The mean relative bioavailability of the nasal spray formulation is 102%, compared to the oral tablet.

Zolmitriptan and its active metabolite display dose proportionality after single or multiple dosing. Dose proportional increases in zolmitriptan and N-desmethyl metabolite C\textsubscript{max} and AUC were observed for 2.5 and 5 mg nasal spray doses. The pharmacokinetics for elimination of zolmitriptan and its active N-desmethyl metabolite are similar 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 (±SD) apparent volume of distribution for zolmitriptan nasal spray formulation is 8.4±3.3 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 5HT<sub>1B/1D</sub> 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 administration.

Excretion
The mean elimination half-life for zolmitriptan and its active N-desmethyl metabolite following nasal spray administration are approximately 3 hours, which is similar to the half-life values seen after oral tablet administration. The half-life values were similar for zolmitriptan and the N-desmethyl metabolite after single (1 day) and multiple (4 day) nasal dosing.

Mean total plasma clearance 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.

Special Populations
Renal Impairment
The effect of renal impairment on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. After orally dosing zolmitriptan, renal clearance was reduced by 25% in patients with severe renal impairment (Clcr >5 &lt;= 25 mL/min) compared to the normal group (Clcr >70 mL/min); no significant change in renal clearance was observed in the moderately renally impaired group (Clcr >26 &lt;=50 mL/min).

Hepatic Impairment
The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. In severely hepatic impaired patients, the mean C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-∞</sub> of zolmitriptan dosed orally were increased 1.5, 2, and 3-fold, respectively, compared to normal. Seven out of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg dose. Because of the similarity in exposure, zolmitriptan tablets and nasal spray should have similar dosage adjustments and should be administered with caution in subjects with liver disease, generally using doses less than 2.5 mg. Doses lower than 5 mg can only be achieved through the use of an oral formulation.

### Indications

ZOLMIST is indicated for acute treatment of migraine with or without aura in adults.

ZOLMIST should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with ZOLMIST, the diagnosis of migraine should be reconsidered before ZOLMIST is administered to treat any subsequent attacks.

ZOLMIST is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine.

Safety and effectiveness of zolmitriptan have not been established for cluster headache, which is present in an older, predominantly male population.

### Dosage And Administration

Administer one dose of ZOLMIST nasal spray 5 mg for the treatment of acute migraine. If the headache returns the dose may be repeated after 2 hours. The effectiveness of a second dose has not been established in placebo-controlled trials. The maximum daily dose should not exceed 10 mg in any 24-hour period. In controlled clinical trials, single doses of 5
mg of zolmitriptan nasal spray were administered into one nostril and were effective for the treatment of acute migraines in adults.

Individuals may vary in response to ZOLMIST nasal spray. The pharmacokinetics of a 5 mg nasal spray dose is smaller to the 5 mg oral formulations. Doses lower than 5 mg can only be achieved through the use of an oral formulation. The choice of dose and route of administration should therefore be made on an individual basis.

The safety of treating the average of more than four headaches in a 30-day period has not been established.

Hepatic Impairment

Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and significant elevation in blood pressure was observed in some patients. Use of a lower dose of an alternate formulation with blood pressure monitoring is recommended.

Contraindications

Ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease.

Cerebrovascular syndromes including (but not limited to) stroke of any type as well as transient ischemic attacks

Peripheral vascular disease including (but not limited to) ischemic bowel disease

Uncontrolled hypertension

ZOLMIST should not be used within 24 hours of treatment with another 5-HT\textsubscript{1} agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide

Hemiplegic or basilar migraine

Concurrent administration of MAO-A inhibitors or use of ZOLMIST within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated

Hypersensitivity to zolmitriptan or any of its inactive ingredients

Warnings And Precautions

General

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events

Zolmitriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease. It is strongly recommended that zolmitriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, zolmitriptan should not be administered. For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of zolmitriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously
received zolmitriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following ZOLMIST, in these patients with risk factors.

It is recommended that patients who are intermittent long term users of zolmitriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use zolmitriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to zolmitriptan.

Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of zolmitriptan. Life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT\textsubscript{1} agonists. Considering the extent of use of 5-HT\textsubscript{1} agonists in patients with migraine, the incidence of these events is extremely low.

Zolmitriptan can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac disease history and with documented absence of coronary artery disease. Because of the close proximity of the events to zolmitriptan use, a causal relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive zolmitriptan. Because of the potential of this class of compound (5-HT\textsubscript{1} agonists) to cause coronary vasospasm, ZOLMIST should not be given to patients with documented ischemic or vasospastic coronary artery disease.

Sensations of Pain, Lightness, Pressure in the Chest And or Throat, Neck, and Jaw
As with other 5-HT\textsubscript{1} agonists, sensation of lightness, pain, pressure, and heaviness in the precordium throat, neck and jaw have been reported after treatment with zolmitriptan tablets. Because 5-HT\textsubscript{1} agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal’s variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms occur. Patients shown to have CAD and those with Prinzmetal’s variant angina should not receive 5-HT\textsubscript{1} agonists.

Cerebrovascular Events
Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT\textsubscript{1} agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. As with other acute migraine therapies, before treating headaches symptoms, care should be taken to exclude other potentially serious neurological conditions. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g. stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events, including Peripheral Vascular Ischemia and Colonic Ischemia
5-HT\textsubscript{1} agonists, including zolmitriptan, may cause vasospastic reactions other than coronary artery vasospasm, such as peripheral and gastrointestinal vascular ischemia with abdominal pain and bloody diarrhea.

Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT\textsubscript{1} agonists. Visual disorders may also be part of a migraine attack. Patients who experience other symptoms or signs suggestive of decreased arterial flow following the use of any 5-HT agonist, such as ischemic bowel syndrome or Raynaud’s syndrome, are candidates for further evaluation.

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
The development of a potentially life-threatening syndrome may occur with triptans including zolmitriptan treatment, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with ZOLMIST and an SSRI (e.g. fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. 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).

Increase in Blood Pressure
As with other 5-HT\textsubscript{1} agonists, significant elevations in systemic blood pressure have been reported on rare occasions with zolmitriptan tablet use, in patients with and without a history of hypertension; very rarely these increases in blood pressure have been associated with significant clinical events. Zolmitriptan is contraindicated in patients with uncontrolled hypertension. In volunteers, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen at 5 mg. In the headache trials, vital signs were measured only in the small in patient study and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of zolmitriptan. An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT\textsubscript{1} agonist in a study evaluating subjects undergoing cardiac catheterization.

Binding to Melanin-Containing Tissues
When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the value measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies including those conducted by the nasal route. Although no systemic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Drug Interactions

**Ergot-containing drugs:** Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and zolmitriptan within 24 hours of each other should be avoided.

**Xylometazoline:** An in vivo drug interaction study with zolmitriptan nasal spray indicated that 1 spray (100μL dose) of xylometazoline (0.1% w/v), a decongestant, administered 30 minutes prior to a 5 mg nasal dose of zolmitriptan did not alter the pharmacokinetics of zolmitriptan.

**Fluoxetine:** The pharmacokinetics of zolmitriptan, as well as its effect on blood pressure, were unaffected by 4 weeks of pretreatment with oral fluoxetine (20 mg/day).

**MAO-A inhibitors:** Following one week of administration of 150 mg bid moclobemide, a specific MAO-A inhibitor, there...
was an increase of about 25% in both $C_{\text{max}}$ and AUC for zolmitriptan and a 3-fold increase in the $C_{\text{max}}$ and AUC of the active N-desmethyl metabolite of zolmitriptan.

Selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for 1 week, had no effect on the pharmacokinetics of zolmitriptan and its metabolite.

Propranolol: $C_{\text{max}}$ and AUC of zolmitriptan increased 1.5-fold after one week of dosing with propranolol (160 mg/day). $C_{\text{max}}$ and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Acetaminophen: A single 1 g dose of acetaminophen does not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, zolmitriptan delayed the $T_{\text{max}}$ of acetaminophen by one hour.

Metoclopramide: A single 10 mg dose of metoclopramide had no effect on the pharmacokinetics of zolmitriptan or its metabolites.

Oral Contraceptives: Retrospective analysis of pharmacokinetic data across studies indicated that mean plasma concentrations of zolmitriptan were generally higher in females taking oral contraceptives compared to those not taking oral contraceptives. Mean $C_{\text{max}}$ and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and $T_{\text{max}}$ was delayed by one-half hour in females taking oral contraceptives. The effect of zolmitriptan on the pharmacokinetics of oral contraceptives has not been studied.

5-HT$_{1B/1D}$ agonists (e.g. triptans): Concomitant use of other 5-HT$_{1B/1D}$ agonists within 24 hours of ZOLMIST treatment is not recommended.

Cimetidine: Following administration of cimetidine, the half-life and AUC of zolmitriptan and its active metabolites were approximately doubled.

Selective Serotonin Reuptake Inhibitors (SSRI’s)/ Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome: Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRI’s) or serotonin norepinephrine reuptake inhibitors (SNRI’s) and triptans.

Patients with Hepatic Impairment

The effect of hepatic disease on pharmacokinetics of Zolmitriptan nasal spray has not been evaluated. After oral administration, Zolmitriptan exposure was increased in patients with severe hepatic impairment and significant elevation in blood pressure was observed in some patient’s. Hence, Zolmitriptan nasal spray should be administered with caution in subjects with liver disease.

Pregnancy Category C

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

Lactation

It is not known whether zolmitriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when zolmitriptan is administered to a nursing woman. Lactating rats dosed with zolmitriptan had levels in milk equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

Pediatric Use

Safety and effectiveness of zolmitriptan in pediatric patients has not been established. Therefore, ZOLMIST is not recommended for use in patients under 18 years of age.

A single, multicenter, double-blind, randomized placebo-controlled study was conducted to evaluate the efficacy of
Zolmitriptan 5 mg nasal spray in the acute treatment of migraine headache in 171 evaluable adolescent subjects 12 to 17 years of age. Efficacy was not established in that study.

Adverse reactions observed in this study were similar in nature and frequency to those reported in zolmitriptan nasal spray adult clinical trials. The most commonly reported adverse reactions (≥2% and < placebo) were dysgeusia (7%), nasal discomfort (3%), dizziness (2%), nasal congestion (2%), nausea (2%), and throat irritation (2%).

Zolmitriptan nasal spray has not been studied in pediatric patients under 12 years of age.

In the postmarketing experience with triptans, including zolmitriptan, there is a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events; those that were reported are similar in nature to those reported rarely in adults.

Geriatric Use

Although the pharmacokinetic disposition of the drug in the elderly is similar to that seen in younger adults, there is no information about the safety and effectiveness of zolmitriptan in this population because patients over age 65 were excluded from the controlled clinical trials.

Undesirable Effects

Serious cardiac events, including myocardial infarction, have occurred following the use of zolmitriptan tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported, in association with drugs of this class, have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

Incidence in Controlled Clinical Trials

Among 464 patients treating single attacks with zolmitriptan nasal spray in a blinded placebo controlled trial, there was a low withdrawal rate related to adverse events: 5 mg (1.3%), and placebo (0.4%). None of the withdrawals were due to a serious event. One patient was withdrawn due to abnormal ECG changes from baseline that were incidentally found 23 days after the last dose of zolmitriptan nasal spray. The most common adverse events in clinical trials for zolmitriptan nasal spray were: unusual taste, paresthesia, hyperesthesia, and dizziness. The adverse events that occurred in ≥ 2% of the 236 patients in the 5 mg dose group of the controlled clinical trial were Hyperesthesia, Paraesthesia, Disorder/Discomfort of nasal cavity, Pain Location Specified, Pain Throat, Tightness Throat, Dry Mouth, Nausea, Dizziness, Somnolence, Unusual Taste, Asthenia. Adverse clinical events occurring in ≥ 1% and < 2% of patients in all attacks of the controlled clinical trial were pain abdominal, pressure throat, vomiting, headache, tightness chest, dysphagia, insomnia, palpitation and reaction aggravation.

Zolmitriptan is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of the patients (18-39 vs. 40-65 years of age), or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of zolmitriptan in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used zolmitriptan nasal spray and reported an event divided by the total
number of patients exposed to zolmitriptan nasal spray (n=3059). Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare adverse events are those occurring in fewer than 1/1,000 patients.

Body
Infrequent was allergic reaction, back pain, chills, cyst, flu syndrome, infection, jaw pain, pressure other, jaw tightening, edema of the face, abnormal laboratory test, neck pain, neoplasm, and neck tightness, chest heaviness, chest pain, and chest pressure. Rare were cellulitis, fever, jaw pressure, and neck heaviness.

Cardiovascular
Infrequent were arrhythmias, hypertension, syncope, thrombophlebitis, and tachycardia. Rare were angina pectoris, bradycardia, atrial fibrillation, myocardial infarct, vasodilation, and vascular disorder.

Digestive
Infrequent were diarrhea, dyspepsia, tongue edema, gastrointestinal disorder, increased saliva, and thirst. Rare were increased appetite, colitis, constipation, eructation, gastritis, gastrointestinal carcinoma, gingivitis, hepatic neoplasia, intestinal obstruction, jaundice, sialadenitis, and stomatitis.

Endocrine System
Rare were hyperthyroidism and thyroid edema.

Hematologic
Infrequent was cyanosis. Rare were ecchymosis, lymphadenopathy and leukopenia.

Metabolic Nutritional
Rare were increased weight, dehydration, and peripheral edema.

Musculoskeletal
Infrequent were arthralgia, joint disorder, and myalgia. Rare were bone pain, osteoporosis, tenosynovitis and twitching.

Nervous System
Infrequent were agitation, amnesia, anxiety, ataxia, abnormal coordination, confusion, depersonalization, depression, hypertonia, insomnia, nervousness, speech disorder, abnormal thinking, tremor, vertigo, and circumoral paresthesia. Rare were apathy, convulsions, abnormal dreams, euphoria, hypertonia, irritability, tardive dyskinesia, manic reaction, neuropathy, and psychosis.

Respiratory
Infrequent were bronchitis, increased cough, dyspnea, epistasis, laryngeal edema, pharyngitis, rhinitis, sinusitis, throat discomfort, and voice alteration. Rare was hiccup, hyperventilation, laryngitis, pneumonia, increased sputum, and yawning.

Skin
Infrequent was pruritus, rash, skin disorder, and sweating. Rare were eczema, erythema, erythema multiform, hair disorder, and neoplasm.

Special Senses
Infrequent were amblyopia, disorder of lacrimation, ear pain, eye pain, parosmia and tinnitus. Rare were conjunctivitis, dry eye, photophobia, and visual field defect.

Urogenital
Infrequent was polyuria and menorrhagia. Rare were breast carcinoma, dysmenorrhea, metrorrhagia, breast neoplasm, unintended pregnancy, suspicious PAP smear, uterine disorder, enlarged uterine fibroids, fibrocystic breast, vaginitis, urogenital neoplasm, cystitis, urinary tract infection, kidney pain, pyelonephritis, urinary frequency, urine impaired, and urinary tract disorder.

The adverse experience profile seen with zolmitriptan nasal spray is similar to that seen with zolmitriptan tablets except
for the occurrence of local adverse effects from the nasal spray.

**Overdosage**

There is no experience with clinical overdose. Volunteers receiving single 50 mg oral doses of zolmitriptan commonly experienced sedation.

The elimination half-life of zolmitriptan is 3 hours 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 hemodialysis or peritoneal dialysis has on the plasma concentrations of zolmitriptan.

**Packaging Information**

ZOLMIST: Amber glass bottle fitted with a metered-dose spray pump unit, containing 7 doses

_Last Updated: Jan 2016_

_Last Reviewed: Jan 2016_

**ZOLMIST Nasal Spray**

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