Rev 09/03 SIC

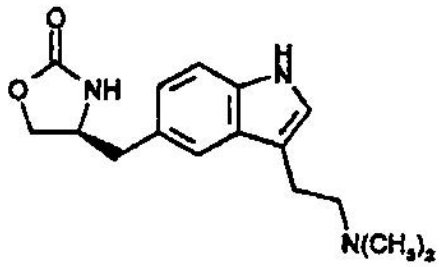
Rx only

# ZOMIG *(zolmitriptan)* Nasal Spray

**For Nasal Use Only**

## DESCRIPTION

ZOMIG® (zolmitriptan) Nasal Spray contains zolmitriptan, which is a selective 5-hydroxytryptamine $_{1B/1D}$ ($5\text{-HT}_{1B/1D}$) receptor agonist. Zolmitriptan is chemically designated as (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone and has the following chemical structure:




The empirical formula is $C_{16}H_{21}N_3O_2$, representing a molecular weight of 287.36. Zolmitriptan is a white to almost white powder that is readily soluble in water. ZOMIG Nasal Spray is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5.0. Each ZOMIG Nasal Spray contains 5 mg of zolmitriptan in a 100-µL unit dose aqueous buffered solution containing citric acid, anhydrous, USP, disodium phosphate dodecahydrate USP and purified water USP.

ZOMIG Nasal Spray is hypertonic. The osmolarity of ZOMIG Nasal Spray 5 mg is 420 to 470 mOsmol.

## CLINICAL PHARMACOLOGY

**Mechanism of Action:** Zolmitriptan binds with high affinity to human recombinant 5-$HT_{1D}$ and 5-$HT_{1B}$ receptors. Zolmitriptan exhibits modest affinity for 5-$HT_{1A}$ receptors, but has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-$HT_2$, 5-$HT_3$, 5-$HT_4$, alpha$_1$-, alpha$_2$- or beta$_1$-adrenergic; $H_1$, $H_2$, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$ receptors. The N-desmethyl metabolite also has high affinity for 5-$HT_{1B/1D}$ and modest 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 for the treatment of migraine headache can most likely be attributed 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.

### Clinical Pharmacokinetics and Bioavailability:

**Absorption:** Zolmitriptan nasal spray is rapidly absorbed via the nasopharynx as detected in a Photon Emission Tomography (PET) study using $^{11}C$ 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 $C_{max}$ 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 10-1000ng/mL. The mean (±SD) apparent volume of distribution for zolmitriptan nasal spray formulation is 8.6±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 $5HT_{1B/1D}$ 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 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**

*Age:* The pharmacokinetics of oral zolmitriptan in healthy elderly non-migraineur volunteers (age 65 - 76 yrs) was similar to those in younger non-migraineur volunteers (age 18-39 yrs).

*Gender:* Mean plasma concentrations of orally administered zolmitriptan were up to 1.5-fold higher in females than males.

*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 ≤ 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 ≤ 50 mL/min).

*Hepatic Impairment:* The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. In severely hepatically impaired patients, the mean $C_{max}$, $T_{max}$, and $AUC_{0-\infty}$ of zolmitriptan dosed orally were increased 1.5, 2, and 3-fold, respectively, compared to normals. 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. (see WARNINGS and PRECAUTIONS).

*Hypertensive Patients:* No differences in the pharmacokinetics of oral zolmitriptan or its effects on blood pressure were seen in mild to moderate hypertensive volunteers compared to normotensive controls.

*Race:* Retrospective analysis of pharmacokinetic data between Japanese and Caucasians revealed no significant differences for orally dosed zolmitriptan.

**Drug Interactions:** All drug interaction studies were performed in healthy volunteers using a single 10 mg dose of zolmitriptan and a single dose of the other drug except where otherwise noted. Eight drug interaction studies have been performed with zolmitriptan tablets and one study (xylometazoline) was performed with nasal spray.

*Xylometazoline:* An in vivo drug interaction study with ZOMIG 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 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 $C_{max}$ and AUC for zolmitriptan and a 3-fold increase in the $C_{max}$ and AUC of the active N-desmethyl metabolite of zolmitriptan (see CONTRAINDICATIONS and PRECAUTIONS).

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:* $C_{max}$ and AUC of zolmitriptan increased 1.5-fold after one week of dosing with propranolol (160 mg/day). $C_{max}$ 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 $T_{max}$ 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 $C_{max}$ and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and $T_{max}$ 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.

*Cimetidine:* Following the administration of cimetidine, the half-life and AUC of a 5 mg dose of zolmitriptan and its active metabolite were approximately doubled (see PRECAUTIONS).

**Clinical Studies:**

The efficacy of ZOMIG Nasal Spray 5 mg in the acute treatment of migraine headache with or without aura was demonstrated in a randomized, outpatient, double-blind, placebo-controlled trial.

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