

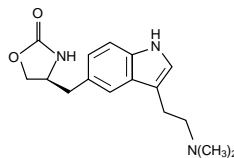
## PROFESSIONAL INFORMATION BROCHURE

# Zomig™

## ZOLMITRIPTAN TABLETS

## DESCRIPTION

ZOMIG™ (zolmitriptan) Tablets contain zolmitriptan, which is a selective 5-hydroxytryptamine<sub>1B</sub> (5-HT<sub>1B</sub>) 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<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>, representing a molecular weight of 287.36. Zolmitriptan is a white to almost white powder that is readily soluble in water. ZOMIG is supplied as 2.5 mg (yellow) and 5 mg (pink) tablets for oral administration. The film-coated tablets contain anhydrous lactose NF, microcrystalline cellulose NF, sodium starch glycolate NF, magnesium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, polyethylene glycol 400 NF, yellow iron oxide NF (2.5 mg tablet), red iron oxide NF (5 mg tablet), and polyethylene glycol 8000 NF.

## CLINICAL PHARMACOLOGY

**Mechanism of Action:** Zolmitriptan binds with high affinity to human recombinant 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. Zolmitriptan exhibits modest affinity for 5-HT<sub>1A</sub> receptors, but has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT<sub>1A</sub>, 5-HT<sub>1C</sub>, 5-HT<sub>1E</sub>, alpha<sub>1</sub>, alpha<sub>2</sub>, or beta<sub>1</sub>-adrenergic; H<sub>1</sub>, H<sub>2</sub>, histaminic; muscarinic; dopaminergic; or dopaminergic receptors. The N-desmethyl metabolite also has high affinity for 5-HT<sub>1B</sub> and modest affinity for 5-HT<sub>1D</sub> 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<sub>1B</sub> 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:** Zolmitriptan is well absorbed after oral administration with peak plasma concentrations occurring in 2 hours. Mean absolute bioavailability is approximately 40%. Zolmitriptan displays linear kinetics over the dose range of 2.5 to 50 mg. The mean elimination half-life of zolmitriptan and its active N-desmethyl metabolite is 3 hours. 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</sub> potency of the metabolite is 2 to 6 times that of the parent, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration. The T<sub>max</sub> for this metabolite is approximately 2 to 3 hours. No accumulation occurred on multiple dosing. Food has no significant effect on the bioavailability of zolmitriptan.

The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan is 25% over the concentration range of 10 - 1000 ng/mL.

Total radioactivity recovered in urine and feces was 65% and 30% of the administered dose, respectively. About 8% of the dose was recovered in the urine as unchanged zolmitriptan. Indole acetic acid metabolite accounted for 31% of the dose, followed by N-oxide (7%) and N-desmethyl (4%) metabolites. The indole acetic acid and N-oxide metabolite are inactive.

Mean total plasma clearance is 31.5 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

During a moderate to severe migraine attack, mean AUC<sub>0-4</sub> and C<sub>max</sub> for zolmitriptan were decreased by 40% and 25%, respectively, and mean T<sub>max</sub> was delayed by one-half hour compared to the same patients during a migraine free period.

## Special Populations

**Age:** Zolmitriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65 - 76 yrs) were similar to those in younger non-migraineur volunteers (age 18 - 39 yrs).

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

**Renal Impairment:** Clearance of zolmitriptan was reduced by 25% in patients with severe renal impairment (Cl<sub>cr</sub> ≤ 25 mL/min) compared to the normal group (Cl<sub>cr</sub> > 70 mL/min); no significant change in clearance was observed in the moderately renally impaired group (Cl<sub>cr</sub> ≥ 26 ≤ 50 mL/min).

**Hepatic Impairment:** In severely hepatically impaired patients, the mean C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-4</sub> of zolmitriptan were increased 1.5, 2 (2 vs. 4 hrs), 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. Zolmitriptan should be administered with caution in subjects with liver disease, generally using doses less than 2.5 mg (See WARNINGS and PRECAUTIONS).

**Hypertensive Patients:** No differences in the pharmacokinetics of 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.

**Drug Interactions:** All drug interaction studies were conducted in healthy volunteers using a single 10 mg dose of zolmitriptan and a single dose of the other drug except where otherwise noted.

**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<sub>max</sub> and AUC for zolmitriptan and a 3-fold increase in the C<sub>max</sub> and AUC of the active N-desmethyl metabolite of zolmitriptan (see CONTRAINDICATIONS and PRECAUTIONS).

**Seligiline:** 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<sub>max</sub> and AUC of Zolmitriptan increased 1.5-fold after one week of dosing with propranolol (160 mg/day). C<sub>max</sub> 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<sub>max</sub> of acetaminophen by one hour.

**Metoprolol:** A single 10 mg dose of metoprolol 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

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were generally higher in females taking oral contraceptives compared to those not taking oral contraceptives. Mean C<sub>max</sub> and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and T<sub>max</sub> 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 Tablets in the acute treatment of migraine headaches was demonstrated in five randomized, double blind, placebo controlled studies, of which 2 utilized the 1 mg dose, 2 utilized the 2.5 mg dose and 4 utilized the 5 mg dose; all studies used the marketed formulation. In study 1, patients treated their headaches in a clinic setting. In the other studies, patients treated their headaches as outpatients. In study 4, patients who had previously used sumatriptan were excluded, whereas in the other studies no such exclusion was applied. Patients enrolled in these 5 studies were predominantly female (82%) and Caucasian (97%) with a mean age of 40 years (range 12-65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed at 1, 2, and, in most studies, 4 hours after dosing. Associated symptoms such as nausea, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post dose. A second dose of ZOMIG Tablets or other medication was allowed 2 to 24 hours after the initial treatment for persistent and recurrent headache. The frequency and time to use of these additional treatments were also recorded. In all studies, the effect of zolmitriptan was compared to placebo in the treatment of a single migraine attack.

In all five studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving ZOMIG Tablets at all doses (except for the 1 mg dose in the smallest study) compared to those who received placebo. In the two studies that evaluated the 1 mg dose, there was a statistically significant greater percentage of patients with headache response at 2 hours in the higher dose groups (2.5 and/or 5 mg) compared to the 1 mg dose group. There were no statistically significant differences between the 2.5 and 5 mg dose groups (or of doses up to 20 mg) for the primary endpoint of headache response at 2 hours in any study. The results of these controlled clinical studies are summarized in Table 1.

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of data under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

Table 1: Percentage of Patients with Headache Response (Mild or Headache) 2 Hours Following Treatment (n=number of patients randomized).

	Placebo	ZOMIG 1.0 mg	ZOMIG 2.5 mg	ZOMIG 5 mg
Study 1*	16% (n=19)	27% (n=22)	NA	60%*# (n=20)
Study 2	19% (n=88)	NA	NA	66%* (n=179)
Study 3	34% (n=121)	50%* (n=140)	65%*# (n=260)	67%*# (n=245)
Study 4*	44% (n=55)	NA	NA	59%* (n=491)
Study 5	36% (n=92)	NA	62%* (n=178)	NA

\* p<0.05 in comparison with placebo.

# p<0.05 in comparison with 1 mg

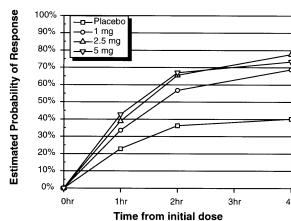
a This was the only study in which patients treated the headache in a clinic setting.

b This was the only study where patients were excluded who had previously used sumatriptan

NA - not applicable

The estimated probability of achieving an initial headache response by 4 hours following treatment is depicted in Figure 1.

Figure 1: Estimated probability of Achieving initial headache response within 4 hours \*

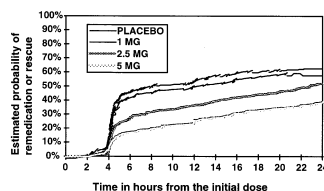


\*Figure 1 shows the Kaplan Meier plot of the probability over time of obtaining headache response (no or mild pain) following treatment with zolmitriptan. The averages displayed are based on pooled data from 3 placebo controlled, outpatient, trials providing evidence of efficacy (Trials 2, 3 and 5). Patients not achieving headache response or taking additional treatment prior to 4 hours were censored at 4 hours.

For patients with migraine associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of ZOMIG as compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: The Estimated Probability Of Patients Taking A Second Dose Or Other Medication For Migraines Over The 24 Hours Following The Initial Dose Of Study Treatment \*



\*This Kaplan-Meier plot is based on data obtained in 3 placebo controlled clinical trials (Study 2, 3 and 5). Patients not using additional treatments were censored at 24 hours. The plot

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includes both patients who had headache response at 2 hours and those who had no response to the initial dose. It should be noted that the protocols did not allow remediation within 2 hours post dose.

The efficacy of ZOMIG was unaffected by presence of aura; duration of headache prior to treatment; relationship to menses; gender; age or weight of the patient; pretreatment nausea or concomitant use of common migraine prophylactic drugs.

**INDICATIONS AND USAGE:** ZOMIG is indicated for the acute treatment of migraine with or without aura in adults.

ZOMIG is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of ZOMIG have not been established for cluster headache, which is present in an older, predominantly male population.

## CONTRAINDICATIONS

ZOMIG should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to 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 (see WARNINGS).

Because ZOMIG may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

ZOMIG should not be used within 24 hours of treatment with another 5-HT<sub>1</sub> agonist, an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

ZOMIG should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO A inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

ZOMIG is contraindicated in patients who are hypersensitive to zolmitriptan or any of its inactive ingredients.

**WARNINGS:** ZOMIG should only be used where a clear diagnosis of migraine has been established.

**Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:** Because of the potential of this class of compounds (5-HT<sub>1B</sub> agonists) to cause coronary vasospasm, ZOMIG should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). 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 (see CONTRAINDICATIONS). Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of ZOMIG Tablets, no documented episodes of myocardial ischemia or infarction were reported. 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 ZOMIG, in these patients with risk factors.

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

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

**Cardiac Events and Fatalities associated with 5HT<sub>1</sub> agonists:** Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of ZOMIG Tablets, no deaths or serious cardiac events were reported. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT<sub>1</sub> agonists. Considering the extent of use of 5-HT<sub>1</sub> agonists in patients with migraine, the incidence of these events is extremely low.

**Postmarketing experience with zolmitriptan:** Serious cardiovascular events including coronary artery vasospasms, transient myocardial ischemia, angina pectoris and myocardial infarction have been reported in association with the use of ZOMIG Tablets. Some of these events occurred in patients who had no finding of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events, almost all had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by zolmitriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of ZOMIG and the onset of the clinical event, the less likely the association is to be causative.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive ZOMIG.

**Cerebrovascular Events and Fatalities with 5HT<sub>1</sub> agonists:** Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT<sub>1</sub> agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agent having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. 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:** 5HT<sub>1</sub> agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5HT<sub>1</sub> agonists.

**Increase in Blood Pressure:** Significant elevations in systemic blood pressure have been reported on rare occasions in patients with and without a history of hypertension treated with 5-HT<sub>1</sub> agonists. Zolmitriptan is contraindicated in patients with uncontrolled hypertension. In volunteers, an increase of 1 and 5 mmHg 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 inpatient study and there was 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. (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT<sub>1</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

## PRECAUTIONS

**General:** As with other 5-HT<sub>1B</sub> agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with ZOMIG in the cranium, throat, neck and jaw. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. Because drugs in this class may cause coronary artery vasospasm,

