HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOMIG or ZOMIG-ZMT safely and effectively. See full prescribing information for ZOMIG or ZOMIG-ZMT.

ZOMIG (zolmitriptan) tablets, for oral use
ZOMIG-ZMT (zolmitriptan), Orally Disintegrating Tablets
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

ZOMIG is a serotonin (5-HT)$_{1B/1D}$ receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults (1)

Limitations of Use:

- Use only after a clear diagnosis of migraine has been established (1)
- Not indicated for the prophylactic therapy of migraine (1)
- Not indicated for the treatment of cluster headache (1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose: 1.25 mg or 2.5 mg (2.1)
- Maximum single dose: 5 mg (2.1)
- May repeat dose after 2 hours if needed; not to exceed 10 mg in any 24-hour period (2.1)
- Do not break ZOMIG Orally Disintegrating Tablets (2.2)
- Moderate or Severe Hepatic Impairment: 1.25 mg recommended (2.3, 8.6)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg functionally-scored (3)
- Tablets: 5 mg (not scored) (3)
- Orally Disintegrating Tablets: 2.5 mg and 5 mg (3)

CONTRAINDICATIONS

- History of coronary artery disease (CAD) or coronary vasospasm (4)
- Symptomatic Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT$_1$ agonist (e.g., another triptan), or an ergotamine-containing medication (4)
- Monoamine oxidase (MAO)-A inhibitor used in past 2 weeks (4)
- Known hypersensitivity to ZOMIG or ZOMIG-ZMT (4)

WARNINGS AND PRECAUTIONS

- *Myocardial Ischemia/Infarction, and Prinzmetal Angina*: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- *Arrhythmias*: Discontinue ZOMIG if occurs (5.2)
- *Chest/Throat/Neck/Jaw Pain, Tightness, and Pressure*: Generally not associated with myocardial ischemia; evaluate for CAD in patients at high risk (5.3)
- *Cerebral Hemorrhage, Subarachnoid Hemorrhage, and Stroke*: Discontinue ZOMIG if occurs (5.4)
- *Gastrointestinal Ischemic Reactions and Peripheral Vasospastic Reactions*: Discontinue ZOMIG if occurs (5.5)
- *Medication Overuse Headache*: Detoxification may be necessary (5.6)
- *Serotonin Syndrome*: Discontinue ZOMIG if occurs (5.7, 7.4)
- *Patients with Phenylketonuria*: ZOMIG-ZMT contains phenylalanine (5.9)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and > placebo) were neck/throat/jaw pain/tightness/pressure, dizziness, paresthesia, asthenia, somnolence, warm/cold sensation, nausea, heaviness sensation, and dry mouth (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories at 1-877-994-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use

- Only use ZOMIG if a clear diagnosis of migraine has been established. If a patient has no response to ZOMIG treatment for the first migraine attack, reconsider the diagnosis of migraine before ZOMIG is administered to treat any subsequent attacks.
- ZOMIG is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of ZOMIG have not been established for cluster headache.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of ZOMIG is 1.25 mg or 2.5 mg. The 1.25 mg dose can be achieved by manually breaking the functionally-scored 2.5 mg tablet in half. The maximum recommended single dose of ZOMIG is 5 mg.

In controlled clinical trials, a greater proportion of patients had headache response following a 2.5 mg or 5 mg dose than following a 1 mg dose. There was little added benefit from the 5 mg dose compared to the 2.5 mg dose, but adverse reactions were more frequent with the 5 mg dose.

If the migraine has not resolved by 2 hours after taking ZOMIG, or returns after a transient improvement, a second dose may be administered at least 2 hours after the first dose. The maximum daily dose is 10 mg in any 24-hour period.

The safety of ZOMIG in the treatment of an average of more than three migraines in a 30-day period has not been established.

2.2 Administration of ZOMIG-ZMT Orally Disintegrating Tablets

Instruct patients not to break ZOMIG-ZMT Orally Disintegrating Tablets because they are not functionally-scored. Administration with liquid is not necessary.

Orally disintegrating tablets are packaged in a blister pack. Instruct patients not to remove the tablet from the blister until just prior to dosing. Subsequently, instruct patients to peel the blister pack open, and to place the orally disintegrating tablet on the tongue, where it will dissolve and it will be swallowed with the saliva.

2.3 Dosing in Patients with Hepatic Impairment

The recommended dose of ZOMIG in patients with moderate to severe hepatic impairment is 1.25 mg (one-half of one 2.5 mg ZOMIG tablet) because of increased zolmitriptan blood levels in these patients and elevation of blood pressure in some of these patients. Limit the total daily dose in patients with severe hepatic impairment to no more than 5 mg per day.

The use of ZOMIG-ZMT Orally Disintegrating Tablets is not recommended in patients with moderate or severe hepatic impairment because these orally disintegrating tablets should not be broken in half *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.4 Dosing in Patients taking Cimetidine

If ZOMIG is co-administered with cimetidine, limit the maximum single dose of ZOMIG to 2.5 mg, not to exceed 5 mg in any 24-hour period *[see Drug Interactions (7.5), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

2.5 mg Tablets: Yellow, biconvex, round, film-coated identified with "ZOMIG" and "2.5" debossed on one side (functionally-scored).

5 mg Tablets: Pink, biconvex, round, film-coated identified with "ZOMIG" and "5" debossed on one side (not scored).

2.5 mg Orally disintegrating tablets: White, flat-faced, round, uncoated, bevelled identified with a debossed "Z" on one side.

5 mg Orally disintegrating tablets: White, flat-faced, round, uncoated, bevelled identified with a debossed "Z" and "5" on one side.

4 CONTRAINDICATIONS

ZOMIG 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 *[see Warnings and Precautions (5.1)]*.
- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Warnings and Precautions (5.2)]*.
- History of stroke, transient ischemic attack (TIA), or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*.
- Peripheral vascular disease (PVD) *[see Warnings and Precautions (5.5)]*.
- Ischemic bowel disease *[see Warnings and Precautions (5.5)]*.
- Uncontrolled hypertension *[see Warnings and Precautions (5.8)]*.
- Recent use (i.e., within 24 hours) of another 5-HT_1 agonist, ergotamine-containing medication, or ergot-type medication (such as dihydroergotamine or methysergide) *[see Drug Interactions (7.1, 7.3)]*.
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent use of a MAO-A inhibitor (that is within 2 weeks) *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.
- Known hypersensitivity to ZOMIG or ZOMIG ZMT (angioedema and anaphylaxis seen) *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal Angina

ZOMIG 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 ZOMIG. Some of these reactions occurred in patients without known CAD. 5-HT_1 agonists including ZOMIG may cause coronary artery vasospasm (Prinzmetal 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 ZOMIG. Do not administer ZOMIG if there is evidence of CAD or coronary artery vasospasm *[see Contraindications (4)]*. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administrating the first ZOMIG dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following ZOMIG administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ZOMIG.

5.2 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-HT_1 agonists. Discontinue ZOMIG if these disturbances occur. ZOMIG is contraindicated in patients with Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Contraindications (4)]*.

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

As with other 5-HT_1 agonists, sensations of tightness, pain, and pressure in the chest, throat, neck, and jaw commonly occur after treatment with ZOMIG and is usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. 5-HT_1 agonists including ZOMIG are contraindicated in patients with CAD or Prinzmetal's variant angina *[see Contraindications (4)]*.

5.4 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.

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, exclude other potentially serious neurological conditions. ZOMIG is contraindicated in patients with a history of stroke or transient ischemic attack *[see Contraindications (4)]*.

5.5 Other Vasospasm Reactions

5-HT_1 agonists, including ZOMIG, 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 a vasospastic reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional ZOMIG doses *[see Contraindications (4)]*.

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.

5.6 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.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including ZOMIG, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors *[see Drug Interactions (7.5)]*. 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. Discontinue ZOMIG if serotonin syndrome is suspected *[see Drug Interactions (7.4)]*.

5.8 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 serious adverse reactions. In healthy subjects treated with 5 mg of ZOMIG, 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 ZOMIG.

As with all triptans, blood pressure should be monitored in ZOMIG-treated patients. ZOMIG is contraindicated in patients with uncontrolled hypertension *[see Contraindications (4)]*.

5.9 Risks in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). ZOMIG-ZMT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 2.5 mg and 5 mg orally disintegrating tablet contains 2.81 and 5.62 mg of phenylalanine, respectively. ZOMIG tablets do not contain phenylalanine.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in other sections of the prescribing information:

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal Angina *[see Warnings and Precautions (5.1)]*.
- Arrhythmias *[see Warnings and Precautions (5.2)]*.
- Chest and or Throat, Neck and Jaw Pain/Tightness/Pressure *[see Warnings and Precautions (5.3)]*.
- Cerebrovascular Events *[see Warnings and Precautions (5.4)]*.
- Other Vasospasm Reactions *[see Warnings and Precautions (5.5)]*.
- Medication Overuse Headache *[see Warnings and Precautions (5.6)]*.
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*.
- Increase in Blood Pressure *[see Warnings and Precautions (5.8)]*.
- Risks in Patients with Phenylketonuria *[see Warnings and Precautions (5.9)]*.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In a long-term, open-label study where patients were allowed to treat multiple migraine attacks for up to 1 year, 8% (167 out of 2,058) withdrew from the trial because of adverse reaction.

The most common adverse reactions (≥5% and > placebo) in these trials were neck/throat/jaw pain, dizziness, paresthesia, asthenia, somnolence, warm/cold sensation, nausea, heaviness sensation, and dry mouth.

Table 1 lists the adverse reactions that occurred in ≥ 2% of the 2,074 patients in any one of the ZOMIG 1 mg, 2.5 mg, or 5 mg dose groups in the controlled clinical trials of ZOMIG in patients with migraines (Studies 1, 2, 3, 4, and 5) *[see Clinical Studies (14)]*. Only adverse reactions that were at least 2% more frequent in a ZOMIG group compared to the placebo group are included.

Several of the adverse reactions appear dose related, notably paresthesia, sensation of heaviness or tightness in chest, neck, jaw, and throat, dizziness, somnolence and possibly asthenia and nausea.

Table 1: Adverse Reaction Incidence in Five Pooled Placebo-Controlled Migraine Clinical Trials*

	Placebo (n=401)	ZOMIG 1 mg (n=163)	ZOMIG 2.5 mg (n=498)	ZOMIG 5 mg (n=1012)
ATYPICAL SENSATIONS	**6%**	**12%**	**12%**	**18%**
Paresthesia (all types)	2%	5%	7%	9%
Warm/cold sensation	4%	6%	5%	7%
PAIN AND PRESSURE SENSATIONS	**7%**	**13%**	**14%**	**22%**
Chest - pain/tightness/pressure and/or heaviness	1%	2%	3%	4%
Neck/throat/jaw - pain/tightness/pressure	3%	4%	7%	10%
Heaviness other than chest or neck	1%	1%	2%	5%
Other- Pressure/tightness/heaviness	0%	2%	2%	2%
DIGESTIVE	**8%**	**11%**	**16%**	**14%**
Dry mouth	2%	5%	3%	3%
Dyspepsia	1%	3%	2%	1%
Dysphagia	0%	0%	0%	2%
Nausea	4%	4%	9%	6%
NEUROLOGICAL	**10%**	**11%**	**17%**	**21%**
Dizziness	4%	6%	8%	10%
Somnolence	3%	5%	6%	8%
Vertigo	0%	0%	0%	2%
OTHER				
Asthenia	3%	5%	3%	9%
Sweating	1%	0%	2%	3%

* Only adverse reactions that were at least 2% more frequent in a ZOMIG group compared to the placebo group are included.

There were no differences in the incidence of adverse reactions in controlled clinical trials in the following subgroups: gender, weight, age, use of prophylactic medications, or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Less Common Adverse Reactions with ZOMIG Tablets:

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled studies, the role of ZOMIG in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Adverse reaction frequencies were calculated as the number of patients who used ZOMIG tablets and reported a reaction divided by the total number of

patients exposed to ZOMIG tablets (n=4,027). Reactions were further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse reactions (those occurring in 1/100 to 1/1,000 patients) and rare adverse reactions (those occurring in less than 1/1,000 patients).

General: Infrequent were allergic reactions.

Cardiovascular: Infrequent were arrhythmias, hypertension, and syncope. Rare was tachycardia.

Neurological: Infrequent were agitation, anxiety, depression, emotional lability and insomnia; Rare were amnesia, hallucinations, and cerebral ischemia.

Skin: Infrequent were pruritus, rash and urticaria.

Urogenital: Infrequent were polyuria, urinary frequency and urinary urgency.

Adverse Reactions with ZOMIG-ZMT Orally Disintegrating Tablets

The adverse reaction profile seen with ZOMIG-ZMT Orally Disintegrating Tablets was similar to that seen with ZOMIG tablets.

6.2 Postmarketing Experience

The following adverse reactions were identified during post approval use of ZOMIG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The reactions enumerated include all except those already listed in the Clinical Trials Experience section above or the Warnings and Precautions section.

Hypersensitivity Reactions:

As with other 5-$HT_{1B/1D}$ agonists, there have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving ZOMIG. ZOMIG is contraindicated in patients with a history of hypersensitivity reaction to ZOMIG.

7 DRUG INTERACTIONS

7.1 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 ZOMIG within 24 hours of each other is contraindicated *[see Contraindications (4)]*.

7.2 MAO-A Inhibitors

MAO-A inhibitors increase the systemic exposure of zolmitriptan and its active N-desmethyl metabolite. Therefore, the use of ZOMIG in patients receiving MAO-A inhibitors is contraindicated *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

7.3 5-$HT_{1B/1D}$ agonists

Concomitant use of other 5-$HT_{1B/1D}$ agonists (including triptans) within 24 hours of ZOMIG treatment is contraindicated because the risk of vasospastic reactions may be additive *[see Contraindications (4)]*.

7.4 Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

Cases of life-threatening serotonin syndrome have been reported during co-administration of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.7)]*.

7.5 Cimetidine

Following administration of cimetidine, the half-life and blood levels of zolmitriptan and its active N-desmethyl metabolite were approximately doubled *[see Clinical Pharmacology (12.3)]*. If cimetidine and ZOMIG are used concomitantly, limit the maximum single dose of ZOMIG to 2.5 mg, not to exceed 5 mg in any 24-hour period *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ZOMIG in pregnant women. In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals resulted in embryolethality and fetal abnormalities (malformations and variations) at clinically relevant exposures *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The estimated rates of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Animal Data

When zolmitriptan was administered to pregnant rats during the period of organogenesis at oral doses of 100, 400, and 1200 mg/kg/day (plasma exposures (AUCs) ≈280, 1100, and 5000 times the human AUC at the maximum recommended human dose (MRHD) of 10 mg/day), there was a dose-related increase in embryolethality. A no-effect dose for embryolethality was not established. When zolmitriptan was administered to pregnant rabbits during the period of organogenesis at oral doses of 3, 10, and 30 mg/kg/day (plasma AUCs ≈1, 11, and 42 times the human AUC at the MRHD), there were increases in embryolethality and in fetal malformations and variations. The no-effect dose for adverse effects on embryofetal development was associated with a plasma AUC similar to that in humans at the MRHD. When female rats were given zolmitriptan during gestation, parturition, and lactation at oral doses of 25, 100, and 400 mg/kg/day (plasma AUCs ≈70, 280, and 1100 times that in human at the MRHD), an increased incidence of hydronephrosis was found in the offspring. The no-effect dose was associated with a plasma AUC ≈280 times that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of zolmitriptan or its metabolites in human milk, the effects on the breastfed infant, or the effects of zolmitriptan and its metabolites on milk production. In rats, oral dosing with zolmitriptan resulted in levels in milk up to 4 times that in maternal plasma.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOMIG and any potential adverse effects on the breastfed infant from ZOMIG or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established. Therefore, ZOMIG is not recommended for use in patients under 18 years of age.

One randomized, placebo-controlled clinical trial of ZOMIG tablets (2.5, 5 and 10 mg) evaluated 696 pediatric patients (aged 12-17 years) with migraines. This study did not demonstrate the efficacy of ZOMIG compared to placebo in the treatment of migraine in adolescents. Adverse reactions in the adolescent patients treated with ZOMIG were similar in nature and frequency to those reported in clinical trials in adults treated with ZOMIG. ZOMIG has not been studied in pediatric patients less than 12 years old.

In the postmarketing experience with triptans, including ZOMIG, there were no additional adverse reactions seen in pediatric patients that were not seen in adults.

8.5 Geriatric Use

Clinical studies of ZOMIG did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of coronary artery disease) prior to receiving ZOMIG *[see Warnings and Precautions (5.1)]*.

The pharmacokinetics of zolmitriptan were similar in geriatric patients (aged > 65 years) compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Hepatic Impairment

After oral ZOMIG administration, zolmitriptan blood levels were increased in patients with moderate to severe hepatic impairment, and significant elevation in blood pressure was observed in some of these patients *[see Warnings and Precautions (5.8)]*. Therefore, adjust the ZOMIG dose and administer with caution in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.3), Clinical Pharmacology (12)]*.

10 OVERDOSAGE

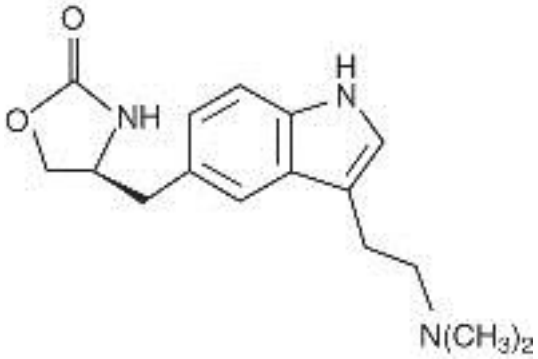
There is no experience with acute overdose of ZOMIG. Clinical study subjects who received single 50 mg oral doses of ZOMIG commonly experienced sedation.

There is no specific antidote to ZOMIG. 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.

The elimination half-life of ZOMIG is 3 hours *[see Clinical Pharmacology (12.1)]*; therefore, monitor patients after overdose with ZOMIG for at least 15 hours or until symptoms or signs resolve. It is unknown what effect hemodialysis or peritoneal dialysis has on the plasma concentrations of zolmitriptan.

11 DESCRIPTION

ZOMIG® (zolmitriptan) tablets and ZOMIG-ZMT® (zolmitriptan) Orally Disintegrating Tablets contain zolmitriptan, which is a selective 5-hydroxytryptamine$_{1B/1D}$ (5-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 tablets are available as 2.5 mg (yellow and functionally-score) and 5 mg (pink, not scored) film-coated 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.

ZOMIG-ZMT® Orally Disintegrating Tablets are available as 2.5 mg and 5 mg white uncoated tablets. The orally disintegrating tablets contain mannitol USP, microcrystalline cellulose NF, crospovidone NF, aspartame NF *[see Warnings and Precautions (5.9)]*, sodium bicarbonate USP, citric acid anhydrous USP, colloidal silicon dioxide NF, magnesium stearate NF and orange flavor SN 027512.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

Migraines are likely 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 ZOMIG 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.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

Absorption

Zolmitriptan is well absorbed after oral administration for both ZOMIG tablets and the ZOMIG-ZMT Orally Disintegrating Tablets. Zolmitriptan displays linear kinetics over the dose range of 2.5 to 50 mg.

The AUC and C_{max} of zolmitriptan are similar following administration of ZOMIG tablets and ZOMIG-ZMT Orally Disintegrating Tablets, but the T_{max} is somewhat later with ZOMIG-ZMT, with a median T_{max} of 3 hours for ZOMIG-ZMT Orally Disintegrating Tablet compared with 1.5 hours for the ZOMIG tablet. The AUC, C_{max}, and T_{max} for the active N-desmethyl metabolite are similar for the two formulations.

During a moderate to severe migraine attack, mean AUC_{0-4} and C_{max} for zolmitriptan, dosed as a ZOMIG tablet, were decreased by 40% and 25%, respectively, and mean T_{max} was delayed by one-half hour compared to the same patients during a migraine free period.

Food has no significant effect on the bioavailability of zolmitriptan. No accumulation occurred on multiple dosing.

Distribution

Mean absolute bioavailability is approximately 40%. 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.

Metabolism

Zolmitriptan is converted to an active N-desmethyl metabolite; 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 ZOMIG administration.

Excretion

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 metabolites 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.

Specific Populations

Hepatic Impairment

In patients with severe hepatic impairment, the mean C_{max}, T_{max}, and $AUC_{0-\infty}$ of zolmitriptan were increased 1.5-fold, 2-fold (2 vs. 4 hours), and 3-fold, respectively, compared to subjects with normal hepatic function. Seven out of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg ZOMIG dose. Adjust the ZOMIG dose in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.3), Use in Specific Populations (8.6)]*.

Renal Impairment

Clearance of zolmitriptan was reduced by 25% in patients with severe renal impairment (Clcr $\geq 5 \leq 25$ mL/min) compared to subjects with normal renal function (Clcr > = 70 mL/min); no significant change in clearance was observed in patients with moderate renal impairment (Clcr $\geq 26 \leq 50$ mL/min).

Age

Zolmitriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65 - 76 years) was similar to those in younger non-migraineur volunteers (age 18 - 39 years).

Sex

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

Race

Retrospective analysis of pharmacokinetic data between Japanese and Caucasians revealed no significant differences.

Hypertensive Patients

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

Drug Interaction Studies

All drug interaction studies were performed in healthy volunteers using a single 10 mg dose of ZOMIG and a single dose of the other drug except where otherwise noted.

MAO Inhibitors

Following one week of administration of moclobemide (150 mg twice daily), 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. MAO inhibitors are contraindicated in ZOMIG-treated patients *[see Contraindications (4), Warnings and Precautions (5.7), Drug Interactions (7.2, 7.4)]*.

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.

Cimetidine

Following the administration of cimetidine, the half-life and AUC of zolmitriptan (5 mg dose), and its active metabolite, were approximately doubled *[see Dosage and Administration (2.4), Drug Interactions (7.5)]*.

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).

Propranolol

C_{max} and AUC of zolmitriptan were 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 changes in blood pressure or pulse rate following administration of propranolol with ZOMIG.

Acetaminophen

A single 1 gram dose of acetaminophen did not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, ZOMIG administration 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 C_{max} and AUC of zolmitriptan were increased by 30% and 50%, respectively, and T_{max} was delayed by one-half hour in women taking oral contraceptives. The effect of ZOMIG on the pharmacokinetics of oral contraceptives has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 approximately 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* mouse 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.

14 CLINICAL STUDIES

ZOMIG Tablets

The efficacy of ZOMIG tablets in the acute treatment of migraine headaches was demonstrated in five randomized, double-blind, placebo-controlled studies (Studies 1, 2, 3, 4, and 5), of which two utilized the 1 mg dose, two utilized the 2.5 mg dose and four utilized the 5 mg dose. 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 ZOMIG 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 who received ZOMIG tablets at all doses (except for the 1 mg dose in the smallest study) compared to those who received placebo. In Studies 1 and 3, 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 end point of headache response at 2 hours in any study. The results of these controlled clinical studies are summarized in Table 2.

Table 2: Percentage of Patients with Headache Response (Reduction in Headache Severity from Moderate or Severe Pain to Mild or No Headache) 2 Hours Following Treatment in Studies 1 through 5

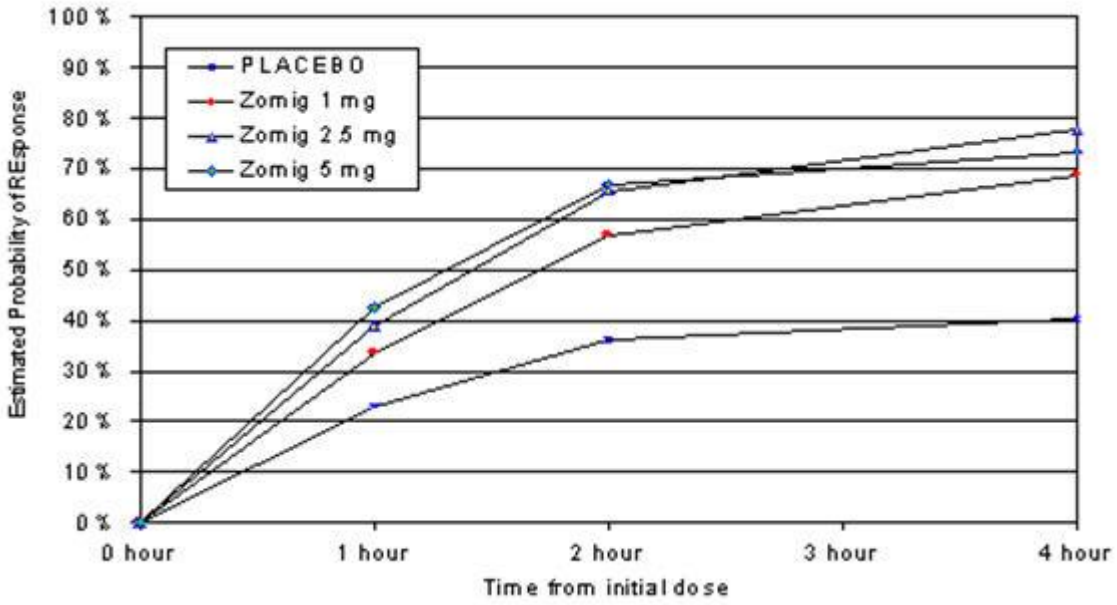
	Placebo	ZOMIG Tablets 1mg	ZOMIG Tablets 2.5 mg	ZOMIG Tablets 5 mg

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

* Study 1 was the only study in which patients treated the headache in a clinic setting.
† n = number of patients randomized
‡ NA = not applicable
§ P<0.05 in comparison with placebo.
¶ P<0.05 in comparison with 1 mg.
# Study 4 was the only study where patients were excluded who had previously used sumatriptan.

The estimated probability of achieving an initial headache response by 4 hours following treatment in pooled Studies 2, 3, and 5 is depicted in Figure 1.

Figure 1 Estimated Probability of Achieving Initial Headache Response (Reduction in Headache Severity from Moderate or Severe Pain to Mild or No Headache) Within 4 Hours of Treatment in Pooled Studies 2, 3, and 5*

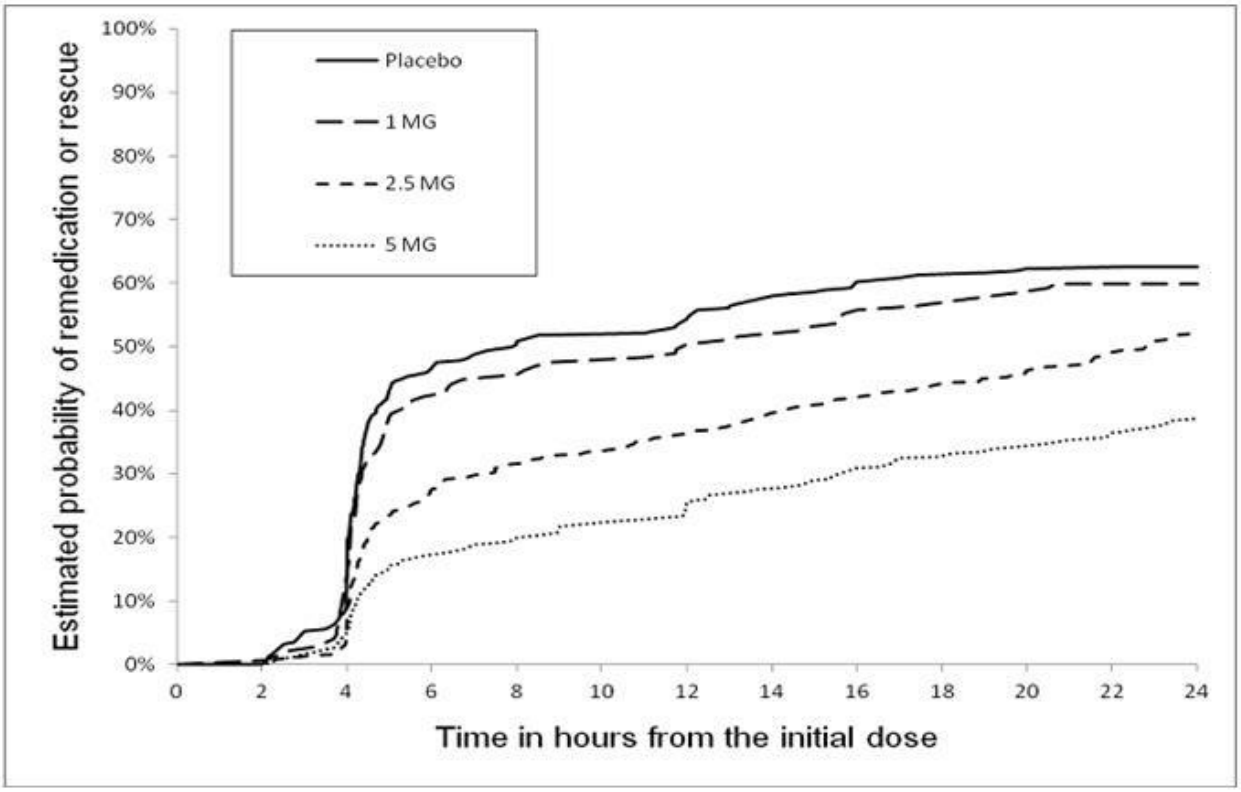


*In this Kaplan-Meier plot, the averages displayed are based on pooled data from 3 placebo controlled, outpatient trials. Patients not achieving headache response or taking additional treatment prior to 4 hours were censored at 4 hours.

For patients with migraine associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of ZOMIG tablets as compared with 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 in Pooled Studies 2, 3, and 5*



*In this Kaplan-Meier plot, patients not using additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. The studies did not allow taking additional doses of study medication within 2 hours post-dose.

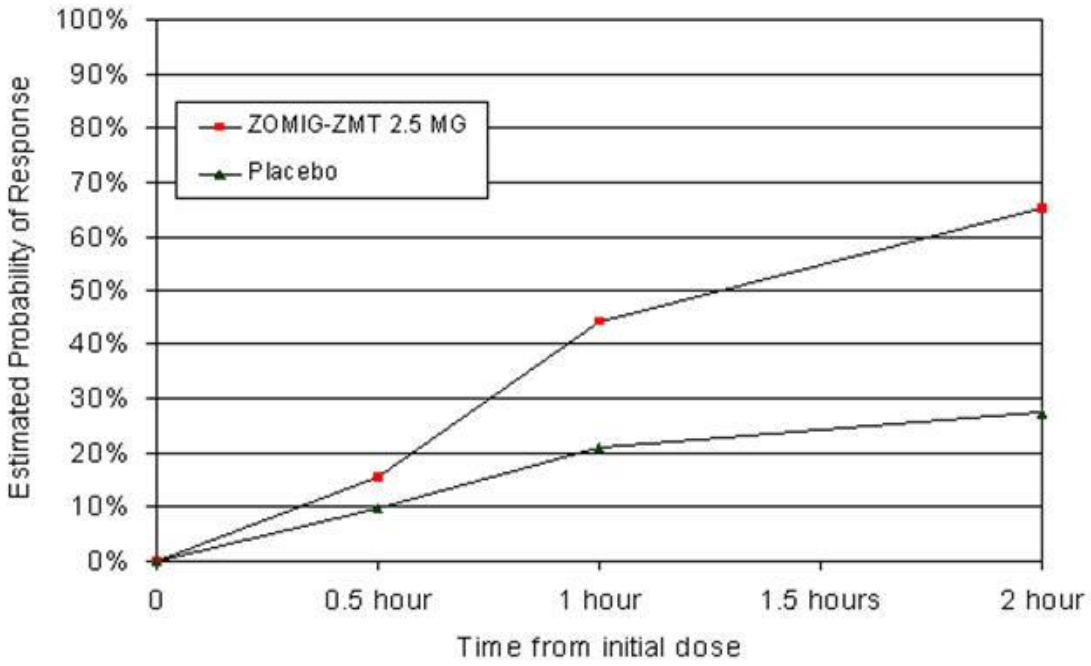
The efficacy of ZOMIG was unaffected by presence of aura; duration of headache prior to treatment; relationship to menses; gender, age, or weight of the patient; pre-treatment nausea or concomitant use of common migraine prophylactic drugs.

ZOMIG-ZMT Orally Disintegrating Tablets

The efficacy of ZOMIG-ZMT 2.5 mg Orally Disintegrating Tablets was demonstrated in a randomized, placebo-controlled trial (Study 6) that was similar in design to the trials of ZOMIG tablets. Patients were instructed to treat a moderate to severe headache. Of the 471 patients treated in Study 6, 87% were female and 97% were Caucasian, with a mean age of 41 years (range 18 - 62).

At 2 hours post-dosing, there was a statistically significant greater percentage of patients treated with ZOMIG-ZMT 2.5 mg with a headache response (reduction in headache severity from moderate or severe pain to mild or no headache) compared to patients treated with placebo (63% vs. 22%). The estimated probability of achieving an initial headache response by 2 hours following treatment with ZOMIG-ZMT Orally Disintegrating Tablets is depicted in Figure 3.

Figure 3 Estimated Probability of Achieving Initial Headache Response (Reduction in Headache Severity from Moderate or Severe Pain to Mild or No Headache) Within 2 Hours in Study 6*

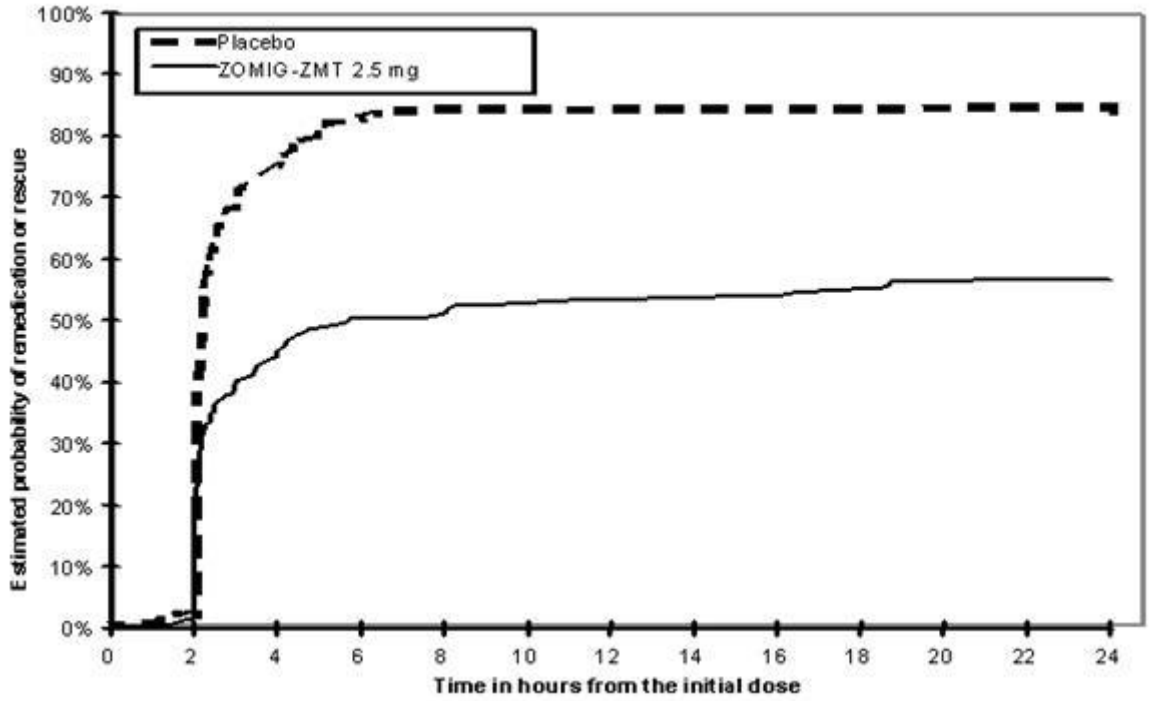


*In this Kaplan-Meier plot patients taking additional treatment or not achieving headache response prior to 2 hours were censored at 2 hours.

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

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment 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 in Study 6 is summarized in Figure 4.

Figure 4 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 in Study 6*



*In this Kaplan-Meier plot, patients not taking additional treatments were censored at 24 hours. The plot includes both patients who had headache response at 2 hours and those who had no response to the initial dose. Taking another dose of study medication was allowed 2 hours post-dose in Study 6. In contrast to studies of ZOMIG tablets (Studies 1, 2, 3, 4, and 5), Study 6 allowed re-dosing of ZOMIG-ZMT Orally Disintegrating Tablets prior to 4 hours.

16 HOW SUPPLIED/STORAGE AND HANDLING

2.5 mg Tablets - Yellow, biconvex, round, film-coated, functionally-scored tablets containing 2.5 mg of zolmitriptan identified with "ZOMIG" and "2.5" debossed on one side are supplied in cartons containing a blister pack of 6 tablets (NDC 64896-671-51).

5 mg Tablets – Pink, biconvex, round, film-coated tablets containing 5 mg of zolmitriptan identified with "ZOMIG" and "5" debossed on one side are supplied in cartons containing a blister pack of 3 tablets (NDC 64896-672-50).

2.5 mg Orally disintegrating tablets - White, flat-faced, round, uncoated, bevelled tablets containing 2.5 mg of zolmitriptan identified with a debossed "Z" on one side are supplied in cartons containing a blister pack of 6 orally disintegrating tablets (NDC 64896-691-51).

5 mg Orally disintegrating tablets - White, flat-faced, round, uncoated, bevelled tablets containing 5 mg of zolmitriptan identified with a debossed "Z" and "5" on one side and plain on the other are supplied in cartons containing a blister pack of 3 orally disintegrating tablets (NDC 64896-692-50).

Store ZOMIG Tablets and ZOMIG-ZMT Tablets at controlled room temperature, 20 - 25ºC (68 - 77ºF) [see USP]. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospastic Reactions, and Cerebrovascular Events

Inform patients that ZOMIG may cause serious cardiovascular adverse reactions such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular reactions can occur without warning

symptoms, instruct patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and instruct them to ask for medical advice when observing any indicative sign or symptoms. Instruct patients to seek medical advice if they have symptoms of other vasospastic reactions *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5)]*.

Medication Overuse Headache

Inform patients that use of drugs to treat acute migraines for 10 or more days per month may lead to an exacerbation of headache, and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) *[see Warnings and Precautions (5.6)]*.

Serotonin Syndrome

Inform patients about the risk of serotonin syndrome with the use of ZOMIG or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.7)]*.

Pregnancy

Advise patients to notify their healthcare provider if they are pregnant or plan to become pregnant.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.2)]*.

Handling of ZOMIG-ZMT Orally Disintegrating Tablets

Inform patients not to break ZOMIG-ZMT Orally Disintegrating Tablets. Inform patients that the orally disintegrating tablet is packaged in a blister. Instruct patients not to remove the orally disintegrating tablet from the blister until just prior to dosing. Instruct patients that prior to dosing, peel open the blister pack and place the orally disintegrating tablet on the tongue, where it will dissolve and be swallowed with the saliva *[see Dosage and Administration (2.2)]*.

Patients with Phenylketonuria

Inform patients with phenylketonuria (PKU) that ZOMIG-ZMT contains phenylalanine (a component of aspartame) *[see Warnings and Precautions (5.9)]*.

Patient Information

ZOMIG® (Zo-mig)
(zolmitriptan)
Tablets

ZOMIG-ZMT® (Zo-mig ZMT)
(zolmitriptan)
Orally Disintegrating Tablets

Please read this information before you start taking ZOMIG and each time you renew your prescription just in case anything has changed. Remember, this summary does not take the place of discussions with your doctor. You and your doctor should discuss ZOMIG when you start taking your medication and at regular checkups.

What is ZOMIG?

ZOMIG is a prescription medication used to treat migraine headaches in adults. ZOMIG is not for other types of headaches. The safety and efficacy of ZOMIG in patients under 18 have not been established.

What is a Migraine Headache?

Migraine is an intense, throbbing headache. You may have pain on one or both sides of your head. You may have nausea and vomiting, and be sensitive to light and noise. The pain and symptoms of a migraine headache can be worse than a common headache. Some women get migraines around the time of their menstrual period. Some people have visual symptoms before the headache, such as flashing lights or wavy lines, called an aura.

How does ZOMIG work?

Treatment with ZOMIG reduces swelling of blood vessels surrounding the brain. This swelling is associated with the headache pain of a migraine attack. ZOMIG blocks the release of substances from nerve endings that cause more pain and other symptoms like nausea, and sensitivity to light and sound. It is thought that these actions contribute to relief of your symptoms by ZOMIG.

Who should not take ZOMIG?

Do not take ZOMIG if you:

- Have heart disease or a history of heart disease
- Have uncontrolled high blood pressure
- Have hemiplegic or basilar migraine (if you are not sure about this, ask your doctor)
- Have or had a stroke or problems with your blood circulation
- Have serious liver problems
- Have taken any of the following medicines in the last 24 hours: other "triptans" like almotriptan (AXERT®), eletriptan (RELPAX®), frovatriptan (FROVA®), naratriptan (AMERGE®), rizatriptan (MAXALT®), sumatriptan (IMITREX®), sumatriptan/naproxen (TREXIMET); ergotamines like BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®; dihydroergotamine like D.H.E. 45® or MIGRANAL®; or methysergide (SANSERT®). These medications have side effects similar to ZOMIG.
- Have taken monoamine oxidase (MAO) inhibitors such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®) for depression or other conditions within the last 2 weeks.
- Are allergic to ZOMIG or any of its ingredients. The active ingredient is zolmitriptan. The inactive ingredients are listed at the end of this leaflet.

Tell your doctor about all the medicines you take or plan to take, including prescription and non-prescription medicines, supplements, and herbal remedies.

Tell your doctor if you are sensitive to phenylalanine, which can be found in the artificial sweetener aspartame. ZOMIG-ZMT contains phenylalanine.

Tell your doctor if you are taking selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), two types of drugs for depression or other disorders. Common SSRIs are CELEXA® (citalopram HBr), LEXAPRO® (escitalopram oxalate), PAXIL® (paroxetine), PROZAC® (fluoxetine), SYMBYAX® (olanzapine/fluoxetine), ZOLOFT® (sertraline), SARAFEM® (fluoxetine) and LUVOX® (fluvoxamine). Common SNRIs are CYMBALTA® (duloxetine) and EFFEXOR® (venlafaxine). Your doctor will decide if you can take ZOMIG with your other medicines.

Tell your doctor if you know that you have any of the following: risk factors for heart disease like high cholesterol, diabetes, smoking, obesity (overweight), menopause, or a family history of heart disease or stroke.

Tell your doctor if you are pregnant or plan to become pregnant. It is not known if ZOMIG will harm your unborn baby.

Tell your doctor if you are breast feeding or plan to breast feed. It is not known if ZOMIG passes into your breast milk. Talk to your doctor about the best way to feed your baby while using ZOMIG.

How should I take ZOMIG?

- Take ZOMIG exactly as your doctor tells you to take it. Your doctor will tell you how much ZOMIG to take and when to take it.
- If you take ZOMIG-ZMT Orally Disintegrating Tablets, do not remove the tablet from the blister pack until you are ready to take your medicine.
- You do not need to take any liquids with your ZOMIG-ZMT Orally Disintegrating Tablets.
- Take ZOMIG-ZMT Orally Disintegrating Tablets whole.
- Place ZOMIG-ZMT Orally Disintegrating Tablets on your tongue, where it will dissolve.
- Safely throw away any unused tablets or pieces of tablets that have been removed from the blister packaging.
- If your headache comes back after your first dose, you may take a second dose any time after 2 hours of taking the first dose. For any attack where the first dose did not work, do not take a second dose without talking with your doctor. Do not take more than a total of 10 mg of ZOMIG (tablets or spray combined in any 24 hour period. If you take too much medicine, contact your doctor, hospital emergency department, or poison control center right away.

What are the possible side effects of ZOMIG?

ZOMIG is generally well tolerated. As with any medicine, people taking ZOMIG may have side effects. The side effects are usually mild and do not last long.

The most common side effects of ZOMIG are:

- pain, pressure or tightness in the neck, throat or jaw
- dizziness
- tingling or other abnormal sensations
- tiredness
- drowsiness
- feeling warm or cold
- nausea
- feeling of tightness or heaviness in other areas of the body
- dry mouth

In very rare cases, patients taking triptans may experience serious side effects, such as heart attacks, high blood pressure, stroke, or serious allergic reactions. Extremely rarely, patients have died. **Call your doctor right away if you have any of the following problems after taking ZOMIG**:

- severe tightness, pain, pressure or heaviness in your chest, throat, neck, or jaw
- shortness of breath or wheezing
- sudden or severe stomach pain
- hives; tongue, mouth, or throat swelling
- problems seeing
- unusual weakness or numbness

Some people may have a reaction called serotonin syndrome, which can be life-threatening, when they use ZOMIG. In particular, this reaction may occur when they use ZOMIG together with certain types of antidepressants known as SSRIs or SNRIs. Symptoms may include mental changes (hallucinations, agitation, coma), fast heartbeat, changes in blood pressure, high body temperature or sweating, tight muscles, trouble walking, nausea, vomiting, and diarrhea. Call your doctor immediately if you have any of these symptoms after taking ZOMIG.

This is not a complete list of side effects. Talk to your doctor if you develop any symptoms that concern you.

What to do in case of an overdose?

Call your doctor or poison control center or go to the nearest hospital emergency room.

General advice about ZOMIG

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ZOMIG for a condition for which it was not prescribed. Do not give ZOMIG to other people, even if they have the same symptoms as you. People may be harmed if they take medicines that have not been prescribed for them.
This leaflet summarizes the most important information about ZOMIG. If you would like more information about ZOMIG, talk to your doctor. You can ask your doctor or pharmacist for information on ZOMIG that is written for healthcare professionals. You can also call 1-877-994-6729 or visit our website at www.ZOMIG.com.

What are the ingredients in ZOMIG?

ZOMIG Tablets
Active ingredient: zolmitriptan
Inactive ingredients: 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

ZOMIG-ZMT Orally Disintegrating Tablets
Active ingredient: zolmitriptan
Inactive ingredients: mannitol USP, microcrystalline cellulose NF, crospovidone NF, aspartame NF, sodium bicarbonate USP, citric acid anhydrous USP, colloidal silicon dioxide NF, magnesium stearate NF and orange flavor SN 027512
Store both ZOMIG Tablets and ZOMIG-ZMT Orally Disintegrating Tablets at controlled room temperature, 68°F to 77°F (20°C to 25°C) and away from children. Protect from light and moisture. Discard when expired.

Distributed by: Impax Specialty Pharma
Hayward, CA 94544
Issued 12/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOMIG Nasal Spray safely and effectively. See full prescribing information for ZOMIG Nasal Spray.

ZOMIG® (zolmitriptan) nasal spray
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE----------

- ZOMIG Nasal Spray is a serotonin $(5\text{-HT})_{1B/1D}$ receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years and older (1)

Limitations of Use:

- Use only after a clear diagnosis of migraine has been established (1)
- Not intended for the prophylactic therapy of migraine (1)
- Not indicated for the treatment of cluster headache (1)
- Not recommended in patients with moderate to severe hepatic impairment (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended starting dose: 2.5 mg (2.1)
- Maximum single dose: 5 mg (2.1)
- May repeat dose after 2 hours if needed; not to exceed 10 mg in any 24-hour period (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal Spray: 2.5 mg and 5 mg (3)

----------CONTRAINDICATIONS----------

- History of ischemic heart disease or coronary artery vasospasm (4)
- Symptomatic Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral Vascular Disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT_1 agonist (e.g., another triptan) or of an ergot-type medication (4)
- MAO-A inhibitor used in past 2 weeks (4)
- Hypersensitivity to ZOMIG (4)

----------WARNINGS AND PRECAUTIONS----------

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue dosing if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue dosing if occurs (5.4)
- Gastrointestinal ischemic events, peripheral vasospastic reactions: Discontinue dosing if occurs (5.5)
- Medication Overuse Headache: Detoxification may be necessary (5.6)
- Serotonin syndrome: Discontinue dosing if occurs (5.7, 7.5)
- Increase in blood pressure: very rarely associated with significant events (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥5% and > placebo) were:

- Adults: unusual taste, paresthesia, dizziness, and hyperesthesia (6.1)
- Pediatrics: unusual taste (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories at 1-877-994-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

If co-administered with cimetidine: Maximum single dose of 2.5 mg, not to exceed 5 mg in any 24-hour period. (2.3, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOMIG Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.

Limitations of Use

- Only use ZOMIG if a clear diagnosis of migraine has been established. If a patient has no response to ZOMIG treatment for the first migraine attack, reconsider the diagnosis of migraine before ZOMIG is administered to treat any subsequent attacks.
- ZOMIG is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of ZOMIG have not been established for cluster headache.
- Not recommended in patients with moderate or severe hepatic impairment [*see Dosage and Administration (2.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose for ZOMIG nasal spray in adult and pediatric patients 12 years of age and older is 2.5 mg. As the individual response to ZOMIG nasal spray may vary, the dose should be adjusted on an individual basis. The maximum recommended single dose of ZOMIG is 5 mg.

If the migraine has not resolved by 2 hours after taking ZOMIG, 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.

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

2.2 Dosing in Patients with Hepatic Impairment

ZOMIG nasal spray is not recommended in patients with moderate to severe hepatic impairment because of increased zolmitriptan blood levels in these patients and elevation of blood pressure in some of these patients. The recommended dosage of ZOMIG nasal spray in patients with mild hepatic impairment is the same as for patients with normal hepatic function [*see Dosage and Administration (2.1), Warnings and Precautions (5.8), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.3 Dosing in Patients taking Cimetidine

If ZOMIG is co-administered with cimetidine, limit the maximum single dose of ZOMIG to 2.5 mg, not to exceed 5 mg in any 24-hour period [*see Drug Interactions (7.4) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray 2.5 mg and 5 mg.

4 CONTRAINDICATIONS

ZOMIG 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 [*see Warnings and Precautions (5.1)*]
- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [*see Warnings and Precautions (5.2)*]
- History of stroke, transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at higher risk of stroke [*see Warnings and Precautions (5.4)*]
- Peripheral vascular disease (PVD) [*see Warnings and Precautions (5.5)*]
- Ischemic bowel disease [*see Warnings and Precautions (5.5)*]
- Uncontrolled hypertension [*see Warnings and Precautions (5.8)*]
- Recent use (i.e., within 24 hours) of another 5-HT_1 agonist, ergotamine-containing medication, or ergot-type medication (such as dihydroergotamine or methysergide) [*see Drug Interactions (7.1, 7.3)*]
- Concurrent administration of an MAO-A inhibitor or recent discontinuation of a MAO-A inhibitor (that is within 2 weeks) [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*]
- Known hypersensitivity to ZOMIG (angioedema and anaphylaxis seen) [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

ZOMIG 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 ZOMIG. Some of these reactions occurred in patients without known CAD. 5-HT_1 agonists including ZOMIG 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 ZOMIG. Do not administer ZOMIG if there is evidence of CAD or coronary artery vasospasm [*see Contraindications (4)*]. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administrating the first ZOMIG dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following ZOMIG administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ZOMIG.

5.2 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-HT_1 agonists. Discontinue ZOMIG if these disturbances occur. Patients with Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive ZOMIG [*see Contraindications (4)*].

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

As with other 5-HT_1 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-HT_1 agonists [*see Contraindications (4)*].

5.4 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 ZOMIG 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. ZOMIG should not be administered to patients with a history of stroke or transient ischemic attack [*see Contraindications (4)*].

5.5 Other Vasospasm Reactions

5-HT_1 agonists, including ZOMIG, 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 ZOMIG doses [*see Contraindications (4)*].

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.

5.6 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.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including ZOMIG, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [*see Drug Interactions (7.5)*]. 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. ZOMIG treatment should be discontinued if serotonin syndrome is suspected [*see Drug Interactions (7.5)* and *Patient Counseling Information (17)*].

5.8 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 ZOMIG 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 ZOMIG oral tablet. As with all triptans, blood pressure should be monitored in ZOMIG-treated patients. ZOMIG is contraindicated in patients with uncontrolled hypertension [*see Contraindications (4)*].

6 ADVERSE REACTIONS

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 (5.1)*]
- Arrhythmias [*see Warnings and Precautions (5.2)*]
- Chest, Throat, Neck and/or Jaw Pain/Tightness/Pressure [*see Warnings and Precautions (5.3)*]
- Cerebrovascular Events [*see Warnings and Precautions (5.4)*]
- Other Vasospasm Reactions [*see Warnings and Precautions (5.5)*]
- Medication Overuse Headache [*see Warnings and Precautions (5.6)*]
- Serotonin Syndrome [*see Warnings and Precautions (5.7)*]
- Increase in Blood Pressure [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adults

Among 460 patients treating 1180 single attacks with ZOMIG nasal spray in a blinded placebo controlled trial (Study 1), there was a low withdrawal rate related to adverse reactions: 5 mg (1.3%), 2.5 mg (0%), 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 ZOMIG nasal spray.

The most common adverse reactions (≥ 5% and > placebo) in any dosage strength in clinical trials for ZOMIG nasal spray were: unusual taste, paresthesia, hyperesthesia, and dizziness. The incidence of adverse reactions was generally dose-related.

Table 1 lists the adverse reactions from the controlled clinical trial (Study 1) that occurred in ≥ 2% of patients in either the 2.5 or 5 mg ZOMIG nasal spray dose groups and with an incidence greater than placebo.

Table 1: Adverse reactions in a Placebo-Controlled Study in Adult Patients with Migraine (Study 1)

Body System Adverse Reaction	**Placebo** **(N=228)**	**ZOMIG 2.5 mg** **(N=224)**	**ZOMIG 5 mg** **(N=236)**
Atypical Sensations			
Hyperesthesia	0%	1%	5%
Paraesthesia	6%	5%	10%
Warm Sensation	2%	4%	0%
Ear/Nose/Throat			
Disorder/Discomfort of nasal cavity	2%	1%	3%
Pain and Pressure Sensations			
Pain Location Specified	1%	2%	4%
Throat Pain	1%	4%	4%
Throat Tightness	1%	<1%	2%
Digestive			
Dry Mouth	<1%	3%	2%
Nausea	1%	1%	4%
Neurological			
Dizziness	4%	6%	3%
Somnolence	2%	1%	4%
Other			

Body System Adverse Reaction	**Placebo** **(N=228)**	**ZOMIG 2.5 mg** **(N=224)**	**ZOMIG 5 mg** **(N=236)**
Unusual Taste	3%	17%	21%
Asthenia	1%	3%	3%

In Study 1, adverse reactions occurring in ≥ 1% and < 2% of patients in all attacks in either ZOMIG nasal spray dose group and with incidence greater than that of placebo were: abdominal pain, chills, throat pressure, facial edema, chest pressure, palpitation, dysphagia, arthralgia, myalgia, and depersonalization.

The incidence of adverse reactions 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 reactions.

Local Adverse Reactions:

Among 460 patients using ZOMIG 2.5 mg or 5 mg in the controlled clinical trial, approximately 3% noted local irritation or soreness at the site of administration. Adverse reactions of any kind, perceived in the nasopharynx (which may include systemic effects of triptans) were severe in about 1% of patients and approximately 57% resolved in 1 hour. Nasopharyngeal examinations, in a subset of patients participating in two long term trials of up to one-year duration, failed to demonstrate any clinically significant changes with repeated use of ZOMIG nasal spray.

All nasopharyngeal adverse reactions with an incidence of ≥ 2% of patients in any ZOMIG nasal spray dose groups are included in Table 1.

Other Adverse Reactions:

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled studies, the role of ZOMIG in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used ZOMIG nasal spray and reported a reaction divided by the total number of patients exposed to ZOMIG nasal spray (n=3059). All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients and rare adverse reactions are those occurring in fewer than 1/1,000 patients.

General: Infrequent: allergic reactions.

Cardiovascular: Infrequent: arrhythmias, hypertension, syncope and tachycardia. Rare: angina pectoris and myocardial infarct.

Digestive: Rare: stomatitis.

Neurological: Infrequent: agitation, amnesia, anxiety, depression, insomnia, and nervousness. Rare: convulsions.

Respiratory: Infrequent: bronchitis, increased cough, dyspnea, epistaxis, laryngeal edema, pharyngitis, rhinitis, and sinusitis.

Skin: Infrequent: pruritus, rash, and urticaria.

Urogenital: Infrequent: polyuria and urinary urgency. Rare: urinary frequency.

Special senses: Infrequent: tinnitus. Rare: conjunctivitis, dry eye, and visual field defect.

The adverse reaction profile seen with ZOMIG nasal spray is similar to that seen with ZOMIG tablets and ZOMIG-ZMT tablets except for the occurrence of local adverse reactions from the nasal spray *(see ZOMIG tablet/ZOMIG-ZMT oral disintegrating tablet Prescribing Information)*.

Pediatric Patients 12 to 17 Years of Age

The safety of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in two studies *[see Pediatric Use (8.4) and Clinical Studies (14.2)]*.

The most common adverse reactions (incidence of ≥ 2% of pediatric patients receiving 2.5 mg and 5 mg ZOMIG nasal spray and numerically greater than placebo) after a single dose are summarized in Table 2. Dysgeusia (unusual taste) was the most common adverse reaction, with a numerically greater incidence for patients receiving ZOMIG compared to placebo (10% vs. 2%). Other common adverse reactions were nasal discomfort, dizziness, oropharyngeal pain, and nausea.

Table 2 lists the adverse reactions from the pooled placebo-controlled studies that occurred in ≥ 2% of pediatric patients 12 to 17 years of age in either the 2.5 mg or 5 mg ZOMIG dose groups and with an incidence greater than placebo.

Table 2: Adverse reactions in Pooled Placebo-Controlled Studies in Pediatric Patients 12 to 17 years of Age with Migraine

Adverse Reaction	Placebo (N=437)	ZOMIG 2.5 mg (N=81)	ZOMIG 5 mg (N=431)
Unusual taste	2%	6%	10%
Nasal discomfort	1%	3%	3%
Dizziness	1%	0%	2%
Oropharyngeal pain	2%	0%	2%
Nausea	1%	1%	2%

The adverse reaction profile was similar across gender. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

6.2 Postmarketing Experience

The following adverse reactions were identified during post approval use of ZOMIG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The reactions enumerated include all except those already listed in the Clinical Trials Experience section above or the Warnings and Precautions section.

Hypersensitivity Reactions:
There have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving ZOMIG. ZOMIG is contraindicated in patients with a history of hypersensitivity reaction to ZOMIG.

7 DRUG INTERACTIONS

7.1 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 ZOMIG within 24 hours of each other is contraindicated [*see Contraindications (4)*].

7.2 MAO-A Inhibitors

MAO-A inhibitors increase the systemic exposure of zolmitriptan. Therefore, the use of ZOMIG in patients receiving MAO-A inhibitors is contraindicated [*see Contraindications (4) and Clinical Pharmacology (12.3)*].

7.3 5-$HT_{1B/1D}$ agonists (e.g. triptans)

Concomitant use of other 5-$HT_{1B/1D}$ agonists (including triptans) within 24 hours of ZOMIG treatment is contraindicated because the risk of vasospastic reactions may be additive [*see Contraindications (4)*].

7.4 Cimetidine

Following administration of cimetidine, the half-life and AUC of ZOMIG and its active metabolites were approximately doubled [*see Clinical Pharmacology (12.3)*]. If cimetidine and ZOMIG are used concomitantly, limit the maximum single dose of ZOMIG to 2.5 mg, not to exceed 5 mg in any 24-hour period [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

7.5 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 [*see Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ZOMIG in pregnant women. In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals resulted in embryolethality and fetal abnormalities (malformations and variations) at clinically relevant exposures *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The estimated rates of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Animal Data

When zolmitriptan was administered to pregnant rats during the period of organogenesis at oral doses of 100, 400, and 1200 mg/kg/day (plasma exposures (AUCs) ≈280, 1100, and 5000 times the human AUC at the maximum recommended human dose (MRHD) of 10 mg/day), there was a dose-related increase in embryolethality. A no-effect dose for embryolethality was not established. When zolmitriptan was administered to pregnant rabbits during the period of organogenesis at oral doses of 3, 10, and 30 mg/kg/day (plasma AUCs ≈1, 11, and 42 times the human AUC at the MRHD), there were increases in embryolethality and in fetal malformations and variations. The no-effect dose for adverse effects on embryo-fetal development was associated with a plasma AUC similar to that in humans at the MRHD. When female rats were given zolmitriptan during gestation, parturition, and lactation at oral doses of 25, 100, and 400 mg/kg/day (plasma AUCs ≈70, 280, and 1100 times that in human at the MRHD), an increased incidence of hydronephrosis was found in the offspring. The no-effect dose was associated with a plasma AUC ≈280 times that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of zolmitriptan or its metabolites in human milk, the effects on the breastfed infant, or the effects of zolmitriptan and its metabolites on milk production. In rats, oral dosing with zolmitriptan resulted in levels in milk up to 4 times that in maternal plasma.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOMIG and any potential adverse effects on the breastfed infant from ZOMIG or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of ZOMIG in pediatric patients under 12 years of age have not been established.

The efficacy of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a placebo-controlled study with a total of 81 pediatric patients receiving ZOMIG 2.5 mg and 229 pediatric patients receiving ZOMIG 5 mg [*see Clinical Studies (14.2)*].

In an earlier study with a different design, ZOMIG 5 mg nasal spray was evaluated in the acute treatment of migraine headache in 171 pediatric patients 12 to 17 years of age. In that study, the efficacy of ZOMIG nasal spray was not established.

The safety of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in two placebo-controlled studies with a total of 81 pediatric patients receiving ZOMIG 2.5 mg and 431 pediatric patients receiving ZOMIG 5 mg [*see Adverse Reactions (6.1)*].

The safety profile of ZOMIG nasal spray in pediatric patients 12 to 17 years of age is similar to the profile observed in adults [*see Adverse Reactions (6.1)*].

In the postmarketing experience with triptans, including ZOMIG, 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.

8.5 Geriatric Use

Clinical studies of ZOMIG did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of coronary artery disease) should have a cardiovascular evaluation prior to receiving ZOMIG [*see Warnings and Precautions (5.1)*]. The pharmacokinetics of zolmitriptan were similar in

geriatric patients (aged > 65 years) compared to younger patients [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. After oral administration, zolmitriptan blood levels were increased in patients with moderate to severe hepatic impairment, and significant elevation in blood pressure was observed in some of these patients [*see Warnings and Precautions (5.8)*]. ZOMIG nasal spray is not recommended in patients with moderate to severe hepatic impairment [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

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

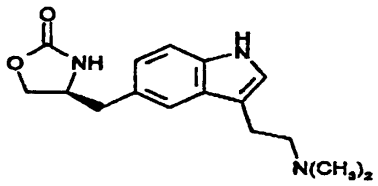
The elimination half-life of ZOMIG is 3 hours [*see Clinical Pharmacology (12.1)*] and therefore monitoring of patients after overdose with ZOMIG should continue for at least 15 hours or while symptoms or signs persist.

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.

11 DESCRIPTION

ZOMIG® (zolmitriptan) Nasal Spray contains zolmitriptan, which is a selective 5-hydroxytryptamine $_{1B/1D}$ (5-$HT_{1B/1D}$) 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 2.5 mg or 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 for 2.5 mg is 360 to 420 mOsmol, and for 5 mg is 420 to 470 mOsmol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 ZOMIG 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.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

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 ZOMIG 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 $5HT_{1B/1D}$ 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 ZOMIG 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.

Specific Populations

Age:

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

Sex:

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

Race:

There are no significant differences in the pharmacokinetics of orally administered zolmitriptan in Japanese and Caucasians.

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 ($Clcr \geq 5 \leq 25$ mL/min) compared with the normal group ($Clcr \geq 70$ mL/min); no significant change in clearance was observed in the moderately renally impaired group ($Clcr \geq 26 \leq 50$ mL/min).

Hepatic Impairment:

The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. In patients with severe hepatic impairment, the mean C_{max}, T_{max}, and AUC of

zolmitriptan dosed orally were increased 1.5-fold, 2-fold (2 vs. 4 hours), and 3-fold, respectively, compared to subjects with normal hepatic function. Seven out of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg ZOMIG dose [*see Dosage and Administration (2.2) and Use in Specific Populations (8.6)*].

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 with normotensive controls.

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 (100 µL 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 pre-treatment with oral fluoxetine (20 mg/day).

MAO Inhibitors:
Following one week of administration of moclobemide (150 mg twice-daily), 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 (4) and Drug Interactions (7.2)*].

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 1g 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 C_{max} and AUC of zolmitriptan were 30% and 50% higher, respectively, and T_{max} was delayed by one-half hour in females taking oral contraceptives compared to females not 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. A dosage adjustment is therefore required [*see Drug Interactions (7.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

14 CLINICAL STUDIES

14.1 Adults

The efficacy of ZOMIG nasal spray 2.5 mg and 5 mg in the acute treatment of migraine headache with or without aura in adults was demonstrated in Study 1, a randomized, outpatient, double-blind, placebo-controlled trial.

In Study 1, 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 15, 30, 45 minutes and 1, 2, and 4 hours after dosing. Pain-free response rates and associated symptoms such as nausea, photophobia, and phonophobia were also assessed. A dose of escape medication was allowed 4 to 24 hours after the initial treatment for persistent and recurrent headache.

In Study 1, of the patients taking ZOMIG nasal spray 2.5 mg or 5 mg, 83% were female and 99% were Caucasian, with a mean age of 41 years (range 18 to 65 years).

The two-hour headache response rates in patients treated with ZOMIG nasal spray were significantly higher among patients receiving ZOMIG nasal spray at all doses, compared with placebo (see Table 3).

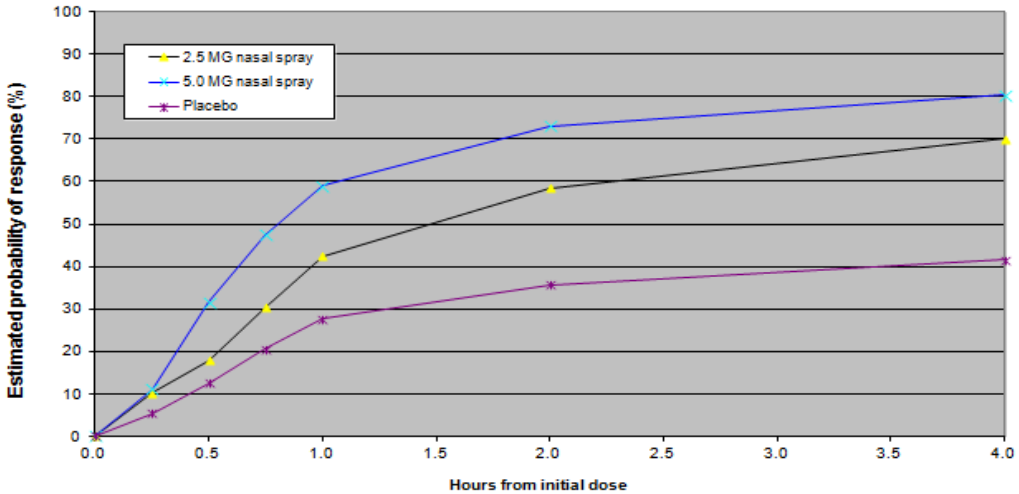
Table 3: First Attack Data: Percentage of Adult Patients with Headache Response to ZOMIG Nasal Spray (Mild or No Headache) 2 Hours Following Treatment in Study 1

PLACEBO (N=218)	ZOMIG 2.5 mg (N=219)	ZOMIG 5 mg (N=228)
31%	55%*	69%*

*p < 0.001 in comparison with placebo

The estimated probability of achieving an initial headache response following treatment with ZOMIG nasal spray is depicted in Figure 1.

Figure 1: Estimated probability of achieving an initial headache response after treatment in Study 1

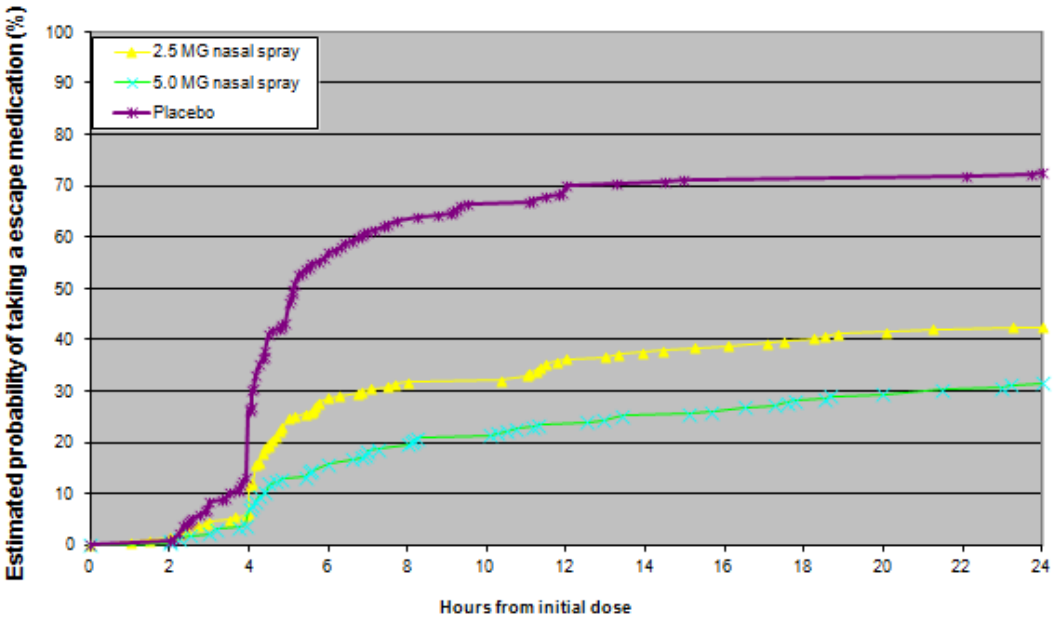


Note: Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache response (moderate or severe headache improving to mild or no pain) following treatment with ZOMIG nasal spray. The estimates displayed are based on a placebo controlled, outpatient trial providing evidence of efficacy. Patients not achieving headache response or taking additional treatment prior to 4 hours were censored to 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 nasal spray as compared with placebo.

Four 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: Estimated probability of patients taking an escape medication within the 24 hours following the initial dose of study treatment in Study 1



*This Kaplan-Meier plot is based on data obtained from the placebo controlled clinical trial. Patients not using additional treatments were censored at 24 hours. The plot 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 protocol did not allow remedication within 4 hours post dose.

The efficacy of ZOMIG was unaffected by presence of aura; presence of headache upon awakening, relationship to menses; gender, age or weight of the patient; or presence of pre-treatment nausea.

The efficacy of ZOMIG nasal spray 5 mg was further supported by an interim analysis of another similarly designed trial. The 2-hour headache response rates for the first 210 subjects in that study for ZOMIG 5 mg and placebo were 70% and 47%, respectively (N=108 and 102, respectively, p=0.0006).

14.2 Pediatric Patients 12 to 17 Years of Age

The efficacy of ZOMIG nasal spray in the acute treatment of migraine headache with or without aura in pediatrics patients 12 to 17 years of age was demonstrated in Study 2, a randomized, double-blind, placebo-controlled trial with a single-blind run-in period.

Patients had to have an established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura with a typical untreated migraine headache attack lasting 3 hours or more. The study included treatment of a single migraine headache attack with 1 dose of single-blind placebo during the 30-day run-in period. If the patient met all conditions for randomization, including a lack of response to the placebo run-in, a subsequent single migraine headache attack was treated with 1 blinded dose of either ZOMIG nasal spray 5 mg, 2.5 mg, or matching placebo.

In Study 2, of the patients taking ZOMIG nasal spray 2.5 mg or 5 mg, 62% were female and 93% were Caucasian, with a mean age of 14 years (range 12 to 17 years).

Study 2 evaluated the proportion of pediatric patients 12 to 17 years of age who had no headache pain at 2 hours following treatment. Headache response (defined as a reduction in migraine-related headache pain severity from moderate or severe pain to mild or no pain) and the absence of nausea, photophobia, and phonophobia at 2 hours post treatment were also assessed. As shown in Table 4, the percentage of pediatric patients 12 to 17 years of age with no headache pain at 2 hours following treatment was significantly higher for ZOMIG nasal spray 5 mg than placebo.

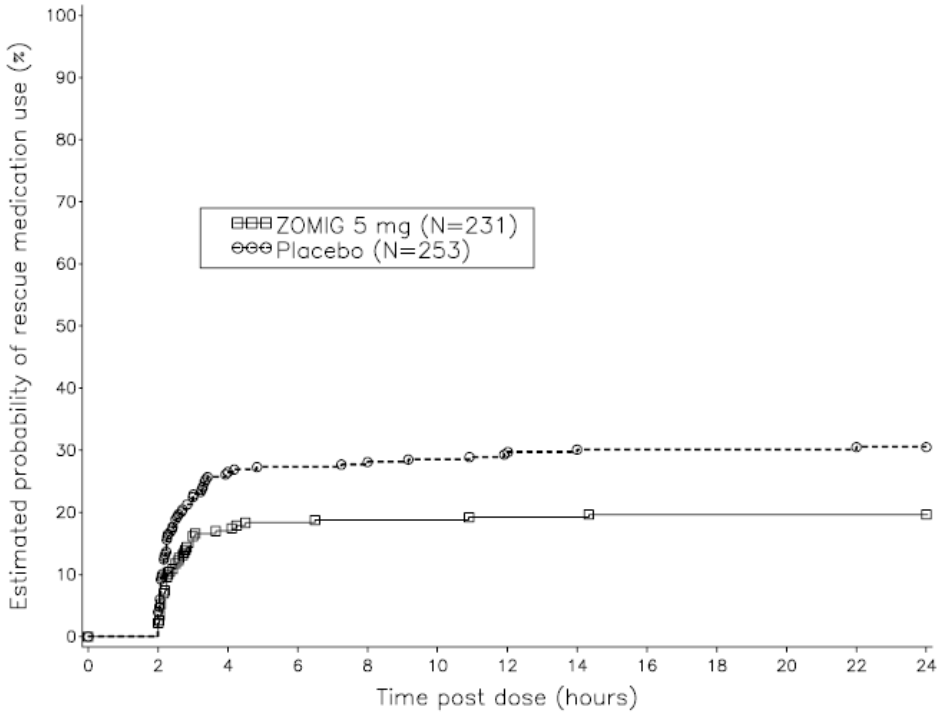
Table 4: Percentage of Pediatric Patients 12 to 17 Years of Age with No Headache Pain, With Headache Response, No Nausea, No Photophobia, and No Phonophobia Two Hours after Treatment in Study 2

Two Hours Following Treatment			
	Placebo (N=253)	**ZOMIG 2.5 mg (N=81)**	**ZOMIG 5 mg (N=229)**
No Headache Pain	17%	25%	30%*
With Headache Response	39%	53%*	51%*
No Photophobia	44%	66%*	56%*
No Phonophobia	48%	61%*	58%*
No Nausea	66%	70%	72%

*$p < 0.05$ in comparison with placebo

Two to 24 hours following the initial dose of study treatment, patients were allowed to use their usual medication for pain relief. The estimated probability of patients taking escape medication during the first 24 hours following the initial dose of study treatment is summarized in Figure 3.

Figure 3: Estimated Probability of Pediatric Patients 12 to 17 Years of Age Taking an Escape Medication Within the 24 Hours Following the Initial Dose of Study Treatment in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

The ZOMIG Nasal Spray device is a blue-colored plastic device with a gray protection cap, labeled to indicate the nominal dose. Each ZOMIG Nasal Spray device administers a single dose of ZOMIG.

ZOMIG Nasal Spray is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5.0. Each ZOMIG Nasal Spray device contains 2.5 mg or 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.

2.5 mg ZOMIG® Nasal Spray is supplied in boxes of 6 single-use nasal spray units. (NDC 64896-682-51)

5 mg ZOMIG® Nasal Spray is supplied in boxes of 6 single-use nasal spray units. (NDC 64896-681-51).

Each ZOMIG® Nasal Spray single dose unit spray supplies 2.5 and 5 mg, respectively, of zolmitriptan. The ZOMIG® Nasal Spray unit must be discarded after use.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's angina, Other Vasospasm-related Events, and Cerebrovascular Events

Inform patients that ZOMIG may cause serious cardiovascular side effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.5)*].

Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache, and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [*see Warnings and Precautions (5.6)*].

Serotonin Syndrome

Inform patients about the risk of serotonin syndrome with the use of ZOMIG or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) [see *Warnings and Precautions (5.7)*].

Pregnancy

Advise patients to notify their healthcare provider if they are pregnant or plan to become pregnant.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [*see Use in Specific Populations (8.2)*].

Handling of ZOMIG nasal spray device

The ZOMIG Nasal Spray device is packaged in a carton and is a blue-colored plastic device with a gray protection cap, labeled to indicate the nominal dose. Caution patients to not remove the gray protection cap until prior to dosing. The ZOMIG Nasal Spray device is placed in a nostril and actuated to deliver a single dose. Caution patients to avoid spraying the contents of the device in their eyes.

Patient Information

ZOMIG® (Zo-mig)
(zolmitriptan)
Nasal Spray

Please read this information before you start taking ZOMIG Nasal Spray and each time you renew your prescription just in case anything has changed. Remember, this summary does not take the place of discussions with your doctor. You and your doctor should discuss ZOMIG Nasal Spray when you start taking your medication and at regular checkups.

What is ZOMIG Nasal Spray?

ZOMIG Nasal Spray is a prescription medicine used to treat migraine headaches with or without aura in adults and pediatric patients (12 to 17 years of age).

ZOMIG Nasal Spray is not for other types of headaches.

ZOMIG Nasal Spray is not for the prevention of migraine headaches.

It is not known if ZOMIG Nasal Spray is safe and effective to treat cluster headaches.

ZOMIG Nasal Spray is not for people with moderate or severe liver problems (hepatic impairment).

It is not known if ZOMIG Nasal Spray is safe and effective in children under 12 years of age.

Who should not use ZOMIG Nasal Spray?
Do not use ZOMIG Nasal Spray if you have:

- heart problems, a history of heart problems, or problems with the electrical system of your heart
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- narrowing of blood vessels to your legs, arms, or stomach (peripheral vascular disease)
- uncontrolled high blood pressure
- used certain medicines called 5-HT_1 agonists ("triptans") such as almotriptan (AXERT®), eletriptan (RELPAX®), frovatriptan (FROVA®), naratriptan (AMERGE®), rizatriptan (MAXALT®), sumatriptan (IMITREX®), sumatriptan/naproxen (TREXIMET®); medicines that contain ergotamine, or ergot medicines such as BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®; dihydroergotamine like D.H.E. 45® or MIGRANAL®; or methysergide (SANSERT®) in the last 24 hours. Ask your doctor or pharmacist for a list of these medicines if you are not sure.
- are taking a monoamine oxidase A inhibitor (MAO-A inhibitor) or you stopped taking a MAO-A inhibitor in the last 14 days. Ask your doctor if you are not sure if you take an MAO-A inhibitor such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®).
- are allergic to zolmitriptan or any of the ingredients in ZOMIG Nasal Spray.
  See the end of this leaflet for a complete list of ingredients in ZOMIG Nasal Spray.

What should I tell my doctor before using ZOMIG Nasal Spray?

Before using ZOMIG Nasal Spray, tell your doctor about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- are a female who has gone through menopause
- have heart disease or a family history of heart disease or stroke
- have liver problems
- are pregnant or plan to become pregnant. It is not known if ZOMIG Nasal Spray will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZOMIG Nasal Spray passes into your breast milk. Talk to your doctor about the best way to feed your baby while using ZOMIG Nasal Spray.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take:

- medicines used to treat mood disorders, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs).
- cimetidine

How should I use ZOMIG NASAL Spray?

For detailed instructions, see the step-by-step instructions for using ZOMIG Nasal Spray at the end of this Patient Information.

- Certain people should take their first dose of ZOMIG Nasal Spray in their doctor's office or in another medical setting. Ask your doctor if you should take your first dose in a medical setting.
- Use ZOMIG Nasal Spray exactly as your doctor tells you to use it.
- Your doctor may change your dose. Do not change your dose without first talking with your doctor.
- If your headache comes back after using one nasal spray or you only get some relief from your headache, you can use another nasal spray 2 hours after the previous nasal spray.
- **Do not** use more than a total of 10 mg of ZOMIG Nasal Spray in any 24-hour period.
- It is not known if it is safe and effective to use ZOMIG Nasal Spray for more than 4 headaches in 30 days.
- Some people who use too much ZOMIG Nasal Spray may have worse headaches (medication overuse headaches). If your headaches get worse, your doctor may decide to stop your treatment with ZOMIG Nasal Spray.
- If you use too much ZOMIG Nasal Spray, call your doctor or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take ZOMIG Nasal Spray so you can talk to your doctor about how ZOMIG Nasal Spray is working for you.

What should I avoid while using ZOMIG Nasal Spray?

ZOMIG Nasal Spray can cause dizziness, weakness, or drowsiness. If you have these symptoms do not drive a car, use machinery, or do anything that needs you to be alert.

What are the possible side effects of ZOMIG Nasal Spray?

ZOMIG Nasal Spray can cause serious side effects.

Call your doctor right away if you have any of the following symptoms after using ZOMIG Nasal Spray:

- **Heart attack and other heart problems.** Heart problems may lead to death. Stop taking ZOMIG Nasal Spray and get emergency medical help right away if you have any of the following symptoms of a heart attack or other heart problems:
  - discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
  - chest pain or chest discomfort that feels like heavy pressure, squeezing, or fullness
  - pain or discomfort in your arms, back, neck, jaw, or stomach
  - shortness of breath with or without chest discomfort
  - breaking out in a cold sweat
  - feeling lightheaded
  - nausea or vomiting with any of the symptoms included above
- **stroke.** Symptoms of stroke include face drooping, slurred speech, and unusual weakness or numbness.
- **changes in color or sensation in your fingers and toes (Raynaud's syndrome)**
- **stomach and intestinal problems** (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- **problems with blood circulation to your legs and feet** (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- **serotonin syndrome.** Serotonin syndrome is a serious and life-threatening problem that can happen in people using ZOMIG Nasal Spray, especially if ZOMIG Nasal Spray is used with anti-depressant medicines called selective serotonin reuptake inhibitors (SSRIs) or selective norephinephrine reuptake inhibitors (SNRIs).

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Call your doctor right away if you have any of the following symptoms of serotonin syndrome:

- mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles
- trouble walking
- nausea, vomiting, or diarrhea

- **increased blood pressure**
- **allergic reactions.** Symptoms of an allergic reaction include:
  - rash
  - hives
  - itching
  - swelling of the face, mouth throat, or tongue
  - difficulty breathing

The most common side effects of ZOMIG Nasal Spray are:

- unusual taste
- numbness
- dizziness
- skin sensitivity (hyperparesthesia)

These are not all the possible side effects of ZOMIG Nasal Spray. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZOMIG Nasal Spray?

Store ZOMIG Nasal Spray at room temperature between 68°F to 77°F (20°C -25°C).

Keep ZOMIG Nasal Spray and all medicines out of the reach of children.

General information about the safe and effective use of ZOMIG Nasal Spray.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use ZOMIG Nasal Spray for a condition for which it was not prescribed. Do not give ZOMIG Nasal Spray to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZOMIG Nasal Spray. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about ZOMIG Nasal Spray that is written for health professionals.

For more information go to www.ZOMIG.com or call 1-877-994-6729.

What are the Ingredients in ZOMIG Nasal Spray?

Active ingredient: zolmitriptan

Inactive ingredients: anhydrous citric acid, dibasic sodium phosphate, and purified water

Instructions for Use

ZOMIG® (Zo-mig)

(zolmitriptan)

Nasal Spray

Important: For use in your nose only. Do not spray in your eyes.

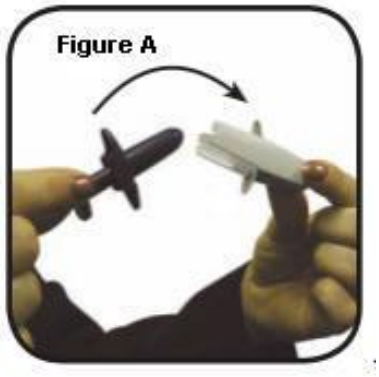
Note: There is only 1 dose in the nasal sprayer. Do not try to prime the nasal sprayer or you will lose the dose. Do not press the plunger until you have put the tip into your nostril or you will lose the dose.

Steps for using ZOMIG Nasal Spray

Step 1. Remove the ZOMIG Nasal Spray unit from the single use package it comes in. Do not remove the unit until you are ready to use it. The unit contains only 1 spray.

Step 2. Blow your nose gently to clear your nasal passages before use.

Step 3. Remove the protective cap **(See Figure A).**



Step 4. Keeping your head in an upright position, gently close 1 nostril with your index finger and breathe out gently through your mouth. **(See Figure B)**. Either nostril can be used.

Step 5. With your other hand, hold the container with your thumb supporting the container at the bottom, and your index and middle fingers on each side of the nozzle. **(See Figure C).**

Insert the tip of the sprayer device into your open nostril as far as feels comfortable and tilt your head slightly **(See Figure D).**

Do not press the plunger yet.

Step 6. Breathe in gently through your nose and at the same time press the plunger firmly with your thumb to release your dose of ZOMIG Nasal Spray **(See Figure D).**

The plunger may feel stiff and you may hear a click. Keep your head slightly tilted back and remove the tip from your nose. Breathe gently through your mouth for 5 to 10 seconds. You may feel liquid in your nose or the back of your throat. This is normal.

Step 7. Dispose the ZOMIG Nasal Spray device after completing the full dose or as soon as it becomes outdated or no longer needed. Dispose of properly. Keep out of reach of children. Do not reuse.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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