

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use zolmitriptan tablets safely and effectively. See full prescribing information for zolmitriptan tablets.**

**ZOLMITRIPTAN tablets, for oral use****Initial US Approval: 1997**

	<b>—RECENT MAJOR CHANGES—</b>
Dosage and Administration (2.1, 2.3, 2.4)	09/2012
Warnings and Precautions (5.6)	09/2012

**—INDICATIONS AND USAGE—**

Zolmitriptan is a serotonin (5-HT)<sub>1B/1D</sub> 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)
- 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)

**—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<sub>1</sub> agonist (e.g., another triptan), or an ergotamine-containing medication (4)
- Monamine oxidase (MAO)-A inhibitor used in past 2 weeks (4)
- Known hypersensitivity to zolmitriptan tablets (4)

**—WARNINGS AND PRECAUTIONS—**

- Myocardial Ischemia/Infarction, and Prinzmetal's Angina:* Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias:* Discontinue zolmitriptan 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 zolmitriptan if occurs (5.4)
- Gastrointestinal Ischemic Reactions and Peripheral Vasospastic Reactions:* Discontinue zolmitriptan if occurs (5.5)
- Medication Overuse Headache:* Detoxification may be necessary (5.6)
- Serotonin Syndrome:* Discontinue zolmitriptan if occurs (5.7, 7.4)

**—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 Jubilant Cadista Pharmaceuticals Inc. at 1-800-313-4623 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: 12/2014**

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

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

**Limitations of Use**

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

**2 DOSAGE AND ADMINISTRATION****2.1 Dosing Information**

The recommended starting dose of zolmitriptan 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 zolmitriptan 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 zolmitriptan, 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 zolmitriptan in the treatment of an average of more than three migraines in a 30-day period has not been established.

**2.3 Dosing in Patients with Hepatic Impairment**

The recommended dose of zolmitriptan in patients with moderate to severe hepatic impairment is 1.25 mg (one-half of one 2.5 mg zolmitriptan 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. [See *Use in Specific Populations* (8.6), and *Clinical Pharmacology* (12.3)].

**2.4 Dosing in Patients taking Cimetidine**

If zolmitriptan is co-administered with cimetidine, limit the maximum single dose of zolmitriptan 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:* Light pink, round, film-coated tablets, debossed with 'CB7' on one side and scoreline on the other side.

*5 mg Tablets:* Light pink, round, film-coated tablets, debossed with 'CB8' on one side and plain on the other side.

**4 CONTRAINDICATIONS**

Zolmitriptan 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<sub>1</sub> 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) and *Clinical Pharmacology* (12.3)]
- Known hypersensitivity to zolmitriptan tablets (angioedema and anaphylaxis seen) [see *Adverse Reactions* (6.2)]

**5 WARNINGS AND PRECAUTIONS****5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina**

Zolmitriptan is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD). There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of zolmitriptan. Some of these reactions occurred in patients without known CAD. 5-HT<sub>1</sub> agonists including zolmitriptan may cause coronary artery vasospasm (Prinzmetal's Angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving zolmitriptan. Do not administer zolmitriptan 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 administering the first zolmitriptan dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following zolmitriptan administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of zolmitriptan.

**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<sub>1</sub> agonists. Discontinue zolmitriptan if these disturbances occur. Zolmitriptan 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<sub>1</sub> agonists, sensations of tightness, pain, and pressure in the chest, throat, neck, and jaw commonly occur after treatment with zolmitriptan and is usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. 5-HT<sub>1</sub> agonists including zolmitriptan 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<sub>1</sub> agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT<sub>1</sub> 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. Zolmitriptan is contraindicated in patients with a history of stroke or transient ischemic attack [see *Contraindications* (4)].

**5.5 Other Vasospasm Reactions**

5-HT<sub>1</sub> agonists, including zolmitriptan, 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<sub>1</sub> agonist, rule out a vasospastic reaction before receiving additional zolmitriptan doses [see *Contraindications* (4)].

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT<sub>1</sub> agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT<sub>1</sub> agonists has 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 zolmitriptan, 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 zolmitriptan 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<sub>1</sub> 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 zolmitriptan, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen. In a study of patients with moderate to severe liver impairment, 7 of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of zolmitriptan.

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

**6 ADVERSE REACTIONS**

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

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's 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)].

**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 zolmitriptan 1 mg, 2.5 mg, or 5 mg dose groups in the controlled clinical trials of zolmitriptan 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 zolmitriptan 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<sup>a</sup>**

	Placebo (n=401)	Zolmitriptan 1 mg (n=163)	Zolmitriptan 2.5 mg (n=498)	Zolmitriptan 5 mg (n=1012)
<b>ATYPICAL SENSATIONS</b>	<b>6%</b>	<b>12%</b>	<b>12%</b>	<b>18%</b>
Paresthesia (all types)	2%	5%	7%	9%
Warm/cold sensation	4%	6%	5%	7%
<b>PAIN AND PRESSURE SENSATIONS</b>	<b>7%</b>	<b>13%</b>	<b>14%</b>	<b>22%</b>
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%
<b>DIGESTIVE</b>	<b>8%</b>	<b>11%</b>	<b>16%</b>	<b>14%</b>
Dry mouth	2%	5%	3%	3%
Dyspepsia	1%	3%	2%	1%
Dysphagia	0%	0%	0%	2%
Nausea	4%	4%	9%	6%
<b>NEUROLOGICAL</b>	<b>10%</b>	<b>11%</b>	<b>17%</b>	<b>21%</b>
Dizziness	4%	6%	8%	10%
Somnolence	3%	5%	6%	8%
<b>OTHER</b>	<b>0%</b>	<b>0%</b>	<b>0%</b>	<b>2%</b>
Vertigo				
Asthenia	3%	5%	3%	9%
Sweating	1%	0%	2%	3%

<sup>a</sup> Only adverse reactions that were at least 2% more frequent in a zolmitriptan 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 Zolmitriptan 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 zolmitriptan 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 zolmitriptan tablets and reported a reaction divided by the total number of patients exposed to zolmitriptan 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 asthenia, hallucinations, and cerebral ischemia.

*Skin:* Infrequent were pruritus, rash and urticaria.

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

***Adverse Reactions with zolmitriptan orally disintegrating tablets:***

The adverse reaction profile seen with zolmitriptan orally disintegrating tablets was similar to that seen with zolmitriptan tablets.

**6.2 Postmarketing Experience**

The following adverse reactions were identified during post approval use of zolmitriptan. 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<sub>1B/1D</sub> agonists, there have been reports of anaphylaxis, anaphylactoid, and hypersensitivity reactions including angioedema in patients receiving zolmitriptan. Zolmitriptan is contraindicated in patients with a history of hypersensitivity reaction to zolmitriptan.

**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 zolmitriptan 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 zolmitriptan in patients receiving MAO-A inhibitors is contraindicated [see *Contraindications* (4) and *Clinical Pharmacology* (12.3)].

**7.3 5-HT<sub>1B/1D</sub> agonists**

Concomitant use of other 5-HT<sub>1B/1D</sub> agonists (including triptans) within 24 hours of zolmitriptan 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 zolmitriptan are used concomitantly, limit the maximum single dose of zolmitriptan to 2.5 mg, not to exceed 5 mg in any 24-hour period [see *Dosage and Administration*, (2.4) and *Clinical Pharmacology* (12.3)].

**8 USE IN SPECIFIC POPULATIONS****8.1 Pregnancy**

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

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] ≈200, 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.

**8.3 Nursing Mothers**

It is not known whether zolmitriptan is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from zolmitriptan, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In rats, oral dosing with zolmitriptan resulted in levels in milk up to 4 times higher than in plasma.

**8.4 Pediatric Use**

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

One randomized, placebo-controlled clinical trial of zolmitriptan 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 zolmitriptan compared to placebo in the treatment of migraine in adolescents. Adverse reactions in the adolescent patients treated with zolmitriptan were similar in nature and frequency to those reported in clinical trials in adults treated with zolmitriptan. Zolmitriptan has not been studied in pediatric patients less than 12 years old.

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

**8.5 Geriatric Use**

Clinical studies of zolmitriptan 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 zolmitriptan [see *Warnings and Precautions*

## What are the possible side effects of zolmitriptan?

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

The most common side effects of zolmitriptan 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 zolmitriptan:**

- **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 zolmitriptan. In particular, this reaction may occur when they use zolmitriptan 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 zolmitriptan.

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

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

## 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 zolmitriptan

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use zolmitriptan for a condition for which it was not prescribed. Do not give zolmitriptan 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 zolmitriptan. If you would like more information about zolmitriptan, talk to your doctor. You can ask your doctor or pharmacist for information on zolmitriptan that is written for healthcare professionals. For more information, call 1-800-313-4623.

## What are the ingredients in Zolmitriptan Tablets?

Active ingredient: zolmitriptan

Inactive ingredients: microcrystalline cellulose, lactose anhydrous, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol 400, polyethylene glycol 8000 (5 mg only), and iron oxide red.

Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

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## Rx Only

### Manufactured by:

Jubilant Generics Limited  
Roorkee-247661, India

### Marketed by:

Jubilant Cadista Pharmaceuticals Inc.  
Salisbury, MD-21801, USA

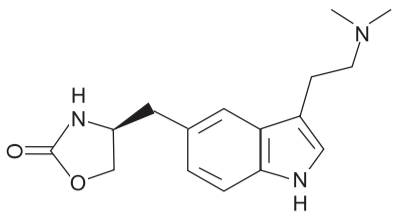
Revised: 12/2014

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 zolmitriptan is 3 hours [See *Clinical Pharmacology* (12.1)]; therefore, monitor patients after overdose with zolmitriptan 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

Zolmitriptan tablets contain zolmitriptan, which is a selective 5-hydroxytryptamine<sub>1B/1D</sub> (5-HT<sub>1B/1D</sub>) receptor agonist. Zolmitriptan is chemically designated as (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone and has the following chemical structure:



The molecular formula is C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>, representing a molecular weight of 287.36. Zolmitriptan is off-white to cream colored crystalline powder that is freely soluble in methanol.

Zolmitriptan tablets are available as 2.5 mg (Light pink and functionally-scored) and 5 mg (Light pink, not scored) film-coated tablets for oral administration. The film-coated tablets contain microcrystalline cellulose, lactose anhydrous, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol 400, polyethylene glycol 8000 (5 mg only), and iron oxide red.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Zolmitriptan binds with high affinity to human recombinant 5-HT<sub>1D</sub> and 5-HT<sub>1B</sub> receptors, and moderate affinity for 5-HT<sub>1A</sub> receptors. The N-desmethyl metabolite also has high affinity for 5-HT<sub>1B/1D</sub> and moderate affinity for 5-HT<sub>1A</sub> 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 zolmitriptan for the treatment of migraine headache is thought to be due to the agonist effects at the 5-HT<sub>1B/1D</sub> receptors on intracranial blood vessels (including the arteriovenous 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 zolmitriptan tablets and the zolmitriptan orally disintegrating tablets. Zolmitriptan displays linear kinetics over the dose range of 2.5 to 50 mg.

The AUC and C<sub>max</sub> of zolmitriptan are similar following administration of zolmitriptan tablets and zolmitriptan orally disintegrating tablets, but the T<sub>max</sub> is somewhat later with zolmitriptan orally disintegrating tablets, with a median T<sub>max</sub> of 3 hours for zolmitriptan orally disintegrating tablets compared with 1.5 hours for the zolmitriptan tablets. The AUC, C<sub>max</sub>, and T<sub>max</sub> for the active N-desmethyl metabolite are similar for the two formulations.

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

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<sub>1B/1D</sub> potency of the metabolite is 2 to 6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration.

##### Excretion

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.

#### Special Populations

##### Hepatic Impairment

In patients with severe hepatic impairment, the mean C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-∞</sub> 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 zolmitriptan dose. Adjust the zolmitriptan dose in patients with moderate or severe hepatic impairment [see *Dosage and Administration* (2.3) and *Use in Specific Populations* (8.6)].

##### Renal Impairment

Clearance of zolmitriptan was reduced by 25% in patients with severe renal impairment (Cl<sub>cr</sub> ≥ 5 < 25 mL/min) compared to subjects with normal renal function (Cl<sub>cr</sub> ≥ 70 mL/min); no significant change in clearance was observed in patients with moderate renal impairment (Cl<sub>cr</sub> ≥ 26 < 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 zolmitriptan 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<sub>max</sub> and AUC for zolmitriptan and a 3-fold increase in the C<sub>max</sub> and AUC of the active N-desmethyl metabolite of zolmitriptan. MAO inhibitors are contraindicated in zolmitriptan-treated patients [see *Contraindications* (4), *Warnings and Precautions* (5.7), and *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<sub>max</sub> and AUC of zolmitriptan were increased 1.5-fold after one week of dosing with propranolol (160 mg/day). C<sub>max</sub> and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no changes in blood pressure or pulse rate following administration of propranolol with zolmitriptan.

##### Acetaminophen

A single 1 gram dose of acetaminophen did not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, zolmitriptan administration delayed the T<sub>max</sub> 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<sub>max</sub> and AUC of zolmitriptan were increased by 30% and 50%, respectively, and T<sub>max</sub> was delayed by one-half hour in women taking oral contraceptives. The effect of zolmitriptan 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 (CHPRT) 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

### Zolmitriptan Tablets

The efficacy of zolmitriptan 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 zolmitriptan tablets or other medication was allowed 2 to 24 hours after the initial treatment for persistent and recurrent headache. The frequency and time to use of these additional treatments were also recorded. In all studies, the effect of zolmitriptan was compared to placebo in the treatment of a single migraine attack.

In all five studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients who received zolmitriptan 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	Zolmitriptan tablets 1 mg	Zolmitriptan tablets 2.5 mg	Zolmitriptan tablets 5 mg
Study 1 <sup>a</sup>	16% (n=19)	27% (n=22)	NA	60%* <sup>#</sup> (n=20)
Study 2	18% (n=88)	NA	NA	66%* (n=179)
Study 3	34% (n=121)	50%* (n=140)	65%* <sup>#</sup> (n=260)	67%* <sup>#</sup> (n=245)
Study 4 <sup>b</sup>	44% (n=55)	NA	NA	59%* (n=491)
Study 5	36% (n=92)	NA	62%* (n=178)	NA

n=number of patients randomized

\* p<0.05 in comparison with placebo.

<sup>#</sup> p<0.05 in comparison with 1 mg.

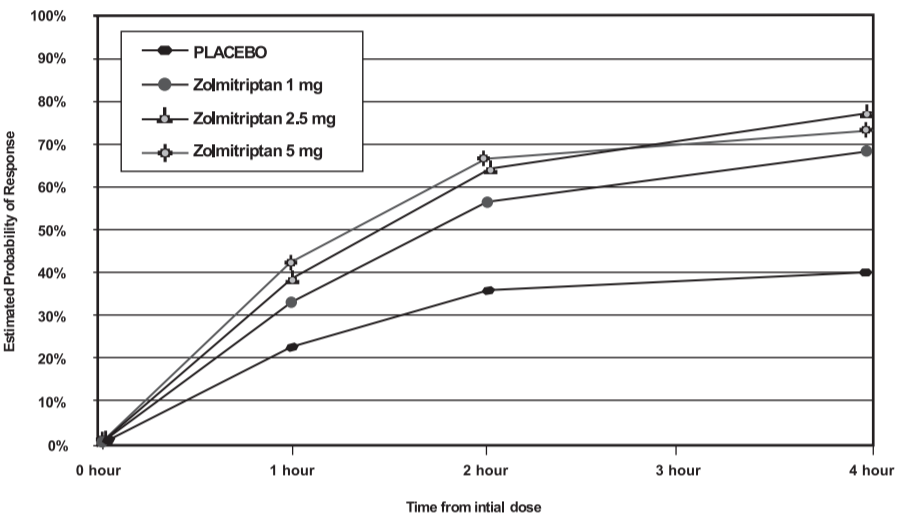
<sup>a</sup> Study 1 was the only study in which patients treated the headache in a clinic setting.

<sup>b</sup> Study 4 was the only study where patients were excluded who had previously used sumatriptan.

NA - not applicable

The estimated probability of achieving an initial headache response by 4 hours following treatment 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\***

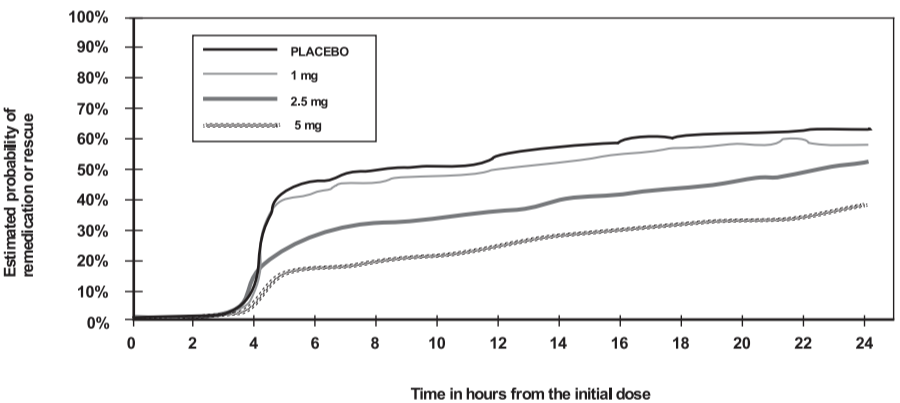


\* In this Kaplan-Meier plot, the averages displayed are based on pooled data from 3 placebo controlled, outpatient trials. Patients not achieving headache response or taking additional treatment prior to 4 hours were censored at 4 hours.

For patients with migraine associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of zolmitriptan 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 zolmitriptan 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.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

**2.5 mg Tablets:** Light pink, round, film-coated tablets, debossed with 'CB7' on one side and scoreline on the other side.

Carton of 3 (1×3) unit-dose tablets NDC 59746-432-13

Carton of 6 (2×3) unit-dose tablets NDC 59746-432-16

**5 mg Tablets:** Light pink, round, film-coated tablets debossed with 'CB8' on one side and plain on the other side.

Carton of 3 (1×3) unit-dose tablets NDC 59746-433-13 (Child resistant pack)

Carton of 6 (2×3) unit-dose tablets NDC 59746-433-16 (Child resistant pack)

Carton of 3 (1×3) unit-dose tablets NDC 59746-433-15 (Non-child resistant pack)

Carton of 6 (2×3) unit-dose tablets NDC 59746-433-17 (Non-child resistant pack)

Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

## 17 PATIENT COUNSELING INFORMATION

See FDA Approved Patient Labeling (Patient Information).

**Myocardial Ischemia and/or Infarction, Prinzmetal's angina, Other Vasospastic Reactions, and Cerebrovascular Events**  
Inform patients that zolmitriptan 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 zolmitriptan 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

Inform patients that zolmitriptan should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations* (8.1)].

## Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [see *Use in Specific Populations* (8.3)].

## Rx Only

### Manufactured by:

Jubilant Generics Limited  
Roorkee-247661, India

### Marketed by:

Jubilant Cadista Pharmaceuticals Inc.  
Salisbury, MD-21801, USA

Revised: 12/2014

<b>Reason for Artwork: New</b>		<b>Dimension: 455 x 530 mm</b>
<b>Item Code: 7524000308</b>		<b>Superseded Item Code: NA</b>
<b>Substrate: 32 GSM Bible paper with folding Dimension 64 x 44 mm</b>		
<b>Site Packaging Development Sign and Date</b>	<b>Production Sign and Date</b>	<b>QA Sign and Date</b>