

ZOLMITRIPTAN- zolmitriptan tablet

Direct_Rx

Zolmitriptan

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

Limitations of Use:

Only use zolmitriptan tablets if a clear diagnosis of migraine has been established. If a patient has no response to zolmitriptan tablets treatment for the first migraine attack, reconsider the diagnosis of migraine before zolmitriptan tablets are administered to treat any subsequent attacks.

Zolmitriptan tablets are not indicated for the prevention of migraine attacks.

Safety and effectiveness of zolmitriptan tablets have not been established for cluster headache.

2.1 Dosing Information

The recommended starting dose of zolmitriptan tablets 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 tablets 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 tablets, 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 tablets 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 tablets in patients with moderate to severe hepatic impairment is 1.25 mg (one-half of one 2.5 mg zolmitriptan tablets) 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.

2.4 Dosing in Patients taking Cimetidine

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

2.5 mg Tablets: Pink, round, biconvex, film-coated tablets with "ZL 1" engraved on one side and break line on other side (functionally-scored).

5 mg Tablets: Yellow, round, biconvex, film-coated tablets with "ZL 2" engraved on one side and plain on other side (not scored).

Zolmitriptan tablets are 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-HT₁ 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 zolmitriptan (angioedema and anaphylaxis seen) [see ADVERSE REACTIONS (6.2)].

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

Zolmitriptan tablets are 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 tablets. Some of these reactions occurred in patients without known CAD. 5-HT₁ agonists including zolmitriptan tablets 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 tablets. Do not administer zolmitriptan tablets 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 tablets dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following zolmitriptan tablets administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of zolmitriptan tablets.

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-HT₁ agonists. Discontinue zolmitriptan tablets if these disturbances occur. Zolmitriptan tablets are 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-HT₁ agonists, sensations of tightness, pain, and pressure in the chest, throat, neck, and jaw commonly occur after treatment with zolmitriptan tablets and is usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. 5-HT₁ agonists including zolmitriptan tablets 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-HT₁ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT₁ 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 tablets are contraindicated in patients with a history of stroke or transient ischemic attack [see CONTRAINDICATIONS (4)].

5.5 Other Vasospasm Reactions

5-HT₁ agonists, including zolmitriptan tablets, 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-HT₁ agonist, rule out a vasospastic reaction before receiving additional zolmitriptan tablets doses [see CONTRAINDICATIONS (4)].

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT₁ agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT₁ 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 tablets, 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 tablets 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-HT₁ 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 tablets, 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 tablets.

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

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 ($\geq 5\%$ 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 $\geq 2\%$ of the 2,074 patients in any one of the zolmitriptan tablets 1 mg, 2.5 mg, or 5 mg dose groups in the controlled clinical trials of zolmitriptan tablets 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 tablets 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*

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

Placebo

(n=401)

Zolmitriptan tablets

1 mg

(n=163)

Zolmitriptan tablets

2.5 mg

(n=498)

Zolmitriptan tablets

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%

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 tablets 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 amnesia, 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 tablets. 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 zolmitriptan tablets. Zolmitriptan tablets are contraindicated in patients with a history of hypersensitivity reaction to zolmitriptan tablets.

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 tablets 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 tablets 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 zolmitriptan tablets 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 tablets are used concomitantly, limit the maximum single dose of zolmitriptan tablets to 2.5 mg, not to exceed 5 mg in any 24-hour period [see DOSAGE AND ADMINISTRATION (2.4), CLINICAL PHARMACOLOGY (12.3)].

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of zolmitriptan tablets in pregnant women. In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals resulted in embryoletality 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) \approx 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 embryoletality. A no-effect dose for embryoletality 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 \approx 1, 11, and 42 times the human AUC at the MRHD), there were increases in embryoletality and in fetal malformations and variations. The no-effect dose for adverse effects on embryofetal development was associated with 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 \approx 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 \approx 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 zolmitriptan tablets and any potential adverse effects on the breastfed infant from zolmitriptan or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established. Therefore, zolmitriptan tablets are 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 tablets compared to placebo in the treatment of migraine in adolescents. Adverse reactions in the adolescent patients treated with zolmitriptan tablets were similar in nature and frequency to those reported in clinical trials in adults treated with zolmitriptan tablets. Zolmitriptan tablets have not been studied in pediatric patients less than 12 years old.

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

8.5 Geriatric Use

Clinical studies of zolmitriptan tablets 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 tablets [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 zolmitriptan tablets 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 zolmitriptan tablets dose and administer with caution in patients with moderate or severe hepatic impairment [see DOSAGE AND ADMINISTRATION (2.3), CLINICAL PHARMACOLOGY (12)].

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

There is no specific antidote to zolmitriptan tablets. 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 zolmitriptan tablets is 3 hours [see CLINICAL PHARMACOLOGY (12.1)]; therefore, monitor patients after overdose with zolmitriptan tablets 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.

Zolmitriptan tablets, USP contain zolmitriptan USP, 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:

[Structure]

The molecular formula is C₁₆H₂₁N₃O₂, representing a molecular weight of 287.36. Zolmitriptan is a white to cream powder that is slightly soluble in water.

Zolmitriptan tablets, USP are available as 2.5 mg (pink) and 5 mg (yellow) film-coated tablets for oral administration. The film-coated tablets contain lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, ferric oxide yellow (2.5 mg and 5 mg tablet), ferric oxide red (2.5 mg tablet).

Zolmitriptan tablets meets USP Dissolution Test 2.

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 zolmitriptan tablets 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 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 zolmitriptan 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 zolmitriptan tablets and zolmitriptan orally disintegrating tablets, but the T_{max} is somewhat later with zolmitriptan orally disintegrating tablets, with a median T_{max} of 3 hours for zolmitriptan orally disintegrating tablets compared with 1.5 hours for the zolmitriptan tablets. 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 AUC₀₋₄ and C_{max} for zolmitriptan, dosed as a zolmitriptan 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 to 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 zolmitriptan tablets 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-∞} 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 tablets dose. Adjust the zolmitriptan 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 (Cl_{cr} ≥ 5 ≤ 25 mL/min) compared to subjects with normal renal function (Cl_{cr} ≥ 70 mL/min); no significant change in clearance was observed in patients with moderate renal impairment (Cl_{cr} ≥ 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 tablets 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 zolmitriptan-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 zolmitriptan tablets.

Acetaminophen

A single 1 gram dose of acetaminophen did not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, zolmitriptan tablets 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 zolmitriptan tablets on the pharmacokinetics of oral contraceptives has not been studied.

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.

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 tablets 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

* 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.

Placebo

Zolmitriptan tablets

1 mg

Zolmitriptan tablets

2.5 mg

Zolmitriptan 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

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*

[figure1]

*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*

[figure2]

*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 tablets 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.

2.5 mg Tablets - Pink, round, biconvex, film-coated tablets with "ZL 1" engraved on one side and break line on other side are supplied in bottles containing 6 tablets (NDC 72189-434-06).

5 mg Tablets - Yellow, round, biconvex, film-coated tablets with "ZL 2" engraved on one

side and plain on other side are supplied in cartons containing 3 tablets (NDC 27241-022-38).

Store zolmitriptan tablets at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

Store zolmitriptan tablets at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

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 zolmitriptan tablets 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 tablets 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)].

Patient Information

Zolmitriptan (zole'' mi trip' tan) Tablets, USP

Please read this information before you start taking zolmitriptan tablets 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 zolmitriptan tablets when you start taking your medication and at regular checkups.

What are zolmitriptan tablets?

Zolmitriptan tablets are a prescription medication used to treat migraine headaches in adults. Zolmitriptan tablets are not for other types of headaches. The safety and efficacy of zolmitriptan tablets 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 zolmitriptan tablets work?

Treatment with zolmitriptan tablets reduces swelling of blood vessels surrounding the brain. This swelling is associated with the headache pain of a migraine attack. Zolmitriptan tablets 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 zolmitriptan tablets.

Who should not take zolmitriptan tablets?

Do not take zolmitriptan tablets 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 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 zolmitriptan tablets.

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 zolmitriptan tablets 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 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 zolmitriptan tablets 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 zolmitriptan tablets will harm your unborn baby.

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

How should I take zolmitriptan tablets?

Take zolmitriptan tablets exactly as your doctor tells you to take it. Your doctor will tell you how much zolmitriptan tablets to take and when to take it.

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 zolmitriptan (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 zolmitriptan tablets?

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

The most common side effects of zolmitriptan tablets 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 tablets:

- 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 tablets. In particular, this reaction may occur

when they use zolmitriptan tablets 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 tablets.

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

You can also contact FDA to report side effects at 1-800-FDA-1088 or 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 tablets

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

What are the ingredients in zolmitriptan tablets?

Zolmitriptan tablets

Active ingredient: zolmitriptan

Inactive ingredients:

lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, ferric oxide yellow (2.5 mg and 5 mg tablet), ferric oxide red (2.5 mg tablet).

Store zolmitriptan tablets at 20-25°C (68-77°F) [see USP Controlled Room Temperature] and away from children. Protect from light and moisture. Discard when expired.

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Marketed by:

Ajanta Pharma USA Inc.

Bridgewater, NJ 08807.

Made in India.

Revised: 01/2019



ZOLMITRIPTAN

zolmitriptan tablet

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|------------------------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:72189-434(NDC:27241-021) |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|----------|
| ZOLMITRIPTAN (UNII: 2FS66TH3YW) (ZOLMITRIPTAN - UNII:2FS66TH3YW) | ZOLMITRIPTAN | 2.5 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|--|----------|
| LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X) | |
| MAGNESIUM STEARATE (UNII: 70097M6I30) | |
| SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2) | |
| TITANIUM DIOXIDE (UNII: 15FIX9V2JP) | |
| POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ) | |
| FERRIC OXIDE RED (UNII: 1K09F3G675) | |
| CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U) | |
| HYPROMELLOSES (UNII: 3NXW29V3WO) | |
| FERRIC OXIDE YELLOW (UNII: EX438O2MRT) | |

Product Characteristics

| | | | |
|-----------------|--------------------------------|---------------------|----------|
| Color | pink | Score | 2 pieces |
| Shape | ROUND ((biconvex,film-coated)) | Size | 7mm |
| Flavor | | Imprint Code | ZL;1 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:72189-434-06 | 6 in 1 BOTTLE; Type 0: Not a Combination Product | 03/13/2023 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA204041 | 03/13/2023 | |

Labeler - Direct_Rx (079254320)

Registrant - Direct_Rx (079254320)

Establishment

| Name | Address | ID/FEI | Business Operations |
|-----------|---------|-----------|---------------------|
| Direct_Rx | | 079254320 | repack(72189-434) |

Revised: 3/2023

Direct_Rx