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

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

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

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

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

---------- DOSAGE FORMS AND STRENGTHS ----------
- Tablets: 2.5 mg functionally-scored (3)
- Tablets: 5 mg (not scored) (3)
- Orally Disintegrating Tablets: 2.5 mg and 5 mg (3)

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

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

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

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

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy: Based on animal data, may cause fetal harm (8.1)

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

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

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

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

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

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

2.2 Administration of ZOMIG-ZMT Orally Disintegrating Tablets

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

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

2.3 Dosing in Patients with Hepatic Impairment

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

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

2.4 Dosing in Patients taking Cimetidine

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

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

4 CONTRAINDICATIONS

ZOMIG is contraindicated in patients with:

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

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal Angina

ZOMIG is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD). There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of ZOMIG. Some of these reactions occurred in patients without known CAD. 5-HT_1 agonists including ZOMIG may cause coronary artery vasospasm (Prinzmetal Angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving ZOMIG. Do not administer ZOMIG if there is evidence of CAD or coronary artery vasospasm *[see Contraindications (4)]*. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administrating the first ZOMIG dose in a medically-supervised setting and performing an electrocardiogram (ECG) immediately following ZOMIG administration. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ZOMIG.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm including ventricular tachycardia and ventricular fibrillation leading to death have been reported within a few hours following the administration of 5-HT_1 agonists. Discontinue ZOMIG if these disturbances occur. ZOMIG is contraindicated in patients with Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders *[see Contraindications (4)]*.

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

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

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with symptoms atypical for migraine, exclude other potentially serious neurological conditions. ZOMIG is contraindicated in patients with a history of stroke or transient ischemic attack *[see Contraindications (4)]*.

5.5 Other Vasospasm Reactions

5-HT_1 agonists, including ZOMIG, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of a vasospastic reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional ZOMIG doses *[see Contraindications (4)]*.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including ZOMIG, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors *[see Drug Interactions (7.5)]*. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually rapidly occurs within minutes to hours of receiving a new or a

greater dose of a serotonergic medication. Discontinue ZOMIG if serotonin syndrome is suspected *[see Drug Interactions (7.4)]*.

5.8 Increase in Blood Pressure

Significant elevations in systemic blood pressure have been reported in patients treated with 5-HT_1 agonists including patients without a history of hypertension; very rarely, these increases in blood pressure have been associated with serious adverse reactions. In healthy subjects treated with 5 mg of ZOMIG, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen. In a study of patients with moderate to severe liver impairment, 7 of 27 patients experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of ZOMIG.

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

5.9 Risks in Patients with Phenylketonuria

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

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