

Telithromycin Targets Respiratory Pathogens

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ORLANDO, FLA. — Telithromycin is an excellent first-line choice for empiric outpatient treatment of mild-to-moderate respiratory tract infections, Carman A. Ciervo, D.O., declared at a satellite symposium held in conjunction with Wonca 2004, the conference of the World Organization of Family Doctors.

The drug, first in the novel ketolide class of antibiotics, has well-established efficacy against the full spectrum of respiratory tract pathogens: the typical and atypical ones, as well as resistant strains. Most importantly, it provides a tailored spectrum of coverage, sparing the primarily enteric gram-negative pathogens such as *Escherichia coli* and *Proteus mirabilis*. This will minimize emergence of resis-



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DR. CIERVO

tance among the gram-negatives that cause important GI and urinary tract infections, explained Dr. Ciervo, chairman of the department of family medicine at the University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine, Stratford.

"I think the advantage that the ketolides have, similar to what the macrolides had in the early '90s, is that they really are a judicious way to prescribe to treat a respiratory tract infection. They cover the bugs that you need to cover for a respiratory tract infection, including the resistant organisms. [However,] I wouldn't be prescribing drugs in this class if I was concerned about diverticulitis or a urinary tract infection, but for the respiratory tract telithromycin is certainly a good choice," added Dr. Ciervo, who is on the speakers' bureau for Aventis, which sponsored the symposium.

Collateral damage to gram-negative pathogens is a significant problem with the fluoroquinolones, with their broad spectrum. It's for this reason that the Centers for Disease Control and Prevention recommends against using the newer fluoroquinolones as first-line therapy in community-acquired pneumonia.

"Better that we reserve them for when we really need them to cover the gram-negatives. When you're treating a respiratory tract infection, why not prescribe an antibiotic that's tailored for patients with respiratory tract infections? That way we can impact future resistance rates of GI tract and urinary pathogens," he continued.

The fluoroquinolones and ketolides share a property that imparts a low propensity to develop resistance: dual binding to the bacterial ribosome. Alteration of the ribosomal binding site is an important mechanism by which bacteria become resistant to antibiotics. This is less likely to

occur when a drug has two binding sites.

Unlike the fluoroquinolones, macrolides, another often-prescribed drug class for respiratory tract infections, don't cause collateral damage to gram-negative pathogens. But they don't cover the full spectrum of respiratory tract pathogens. Macrolides have poor activity against penicillin-nonsusceptible *Streptococcus pneumoniae*, and the incidence of such infections in the United States has been on a steady rise since the mid-1990s.

Macrolide-resistant *S. pneumoniae* is also an emerging problem. It appears to be promoted by use of macrolides having a very long half-life. Azithromycin, for example, has a 72-hour half-life and, consequently, a high potential to select for resistance due to prolonged exposure to subtherapeutic drug concentrations. Telithromycin, in contrast, has a 10-hour half-life.

Telithromycin features once-daily dosing and a 5-day treatment course. There is a growing appreciation that patient com-

pliance falls off dramatically with dosing more than once daily or for more than 5 days, Dr. Ciervo said.

In response to a question, he described doxycycline as "an important and underutilized option" for respiratory tract infections in younger patients—say, those aged 15-50 years—without comorbidity or other significant risk factors for resistant infection, such as having children in day care, chronic renal insufficiency, or recent history of beta-lactam therapy. ■

ZOMIG® (zolmitriptan) Tablets ZOMIG-ZMT™ (zolmitriptan) Orally Disintegrating Tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: ZOMIG is indicated for the acute treatment of migraine with or without aura in adults. ZOMIG is not intended for the prophylactic treatment of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of ZOMIG have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS: ZOMIG should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant, or other significant underlying cardiovascular disease (see WARNINGS). Because ZOMIG may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS). ZOMIG should not be used within 24 hours of treatment with another 5-HT₁ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

ZOMIG should not be administered to patients with hemiplegic or basilar migraine. Concurrent administration of MAO-A inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions). ZOMIG is contraindicated in patients who are hypersensitive to zolmitriptan or any of its inactive ingredients.

WARNINGS: ZOMIG should only be used where a clear diagnosis of migraine has been established. Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: ZOMIG should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that zolmitriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, zolmitriptan should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of zolmitriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received zolmitriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following ZOMIG, in these patients with risk factors. It is recommended that patients who are intermittent long-term users of ZOMIG and who have risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use ZOMIG. The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to zolmitriptan.

Cardiac Events and Fatalities: Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of zolmitriptan. Life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT₁ agonists. Considering the extent of use of 5-HT₁ agonists in patients with migraine, the incidence of these events is extremely low. ZOMIG can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac disease history and with documented absence of coronary artery disease. Because of the close proximity of the events to ZOMIG use, a causal relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain. Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive ZOMIG.

Premarketing experience with zolmitriptan: Among the more than 2,500 patients with migraine who participated in premarketing clinical trials of ZOMIG Tablets, no deaths or serious cardiac events were reported.

Postmarketing experience with zolmitriptan: Serious adverse cardiac events have been reported in association with the use of ZOMIG Tablets, and in very rare cases, in the absence of known cardiovascular disease. The uncontrolled nature of post-marketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by zolmitriptan or to reliably assess causation in individual cases.

Cerebrovascular Events and Fatalities with 5-HT₁ agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported 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 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT₁ agonists may cause vasospastic reactions other than coronary artery vasospasm such as peripheral and gastrointestinal vascular ischemia. As with other serotonin 5-HT₁ agonists, very rare gastrointestinal ischemic events including ischemic colitis and gastrointestinal infarction or necrosis have been reported with ZOMIG Tablets; these may present as bloody diarrhea or abdominal pain.

Increase in Blood Pressure: As with other 5-HT₁ agonists, significant elevations in systemic blood pressure have been reported on rare occasions with ZOMIG Tablets. In a study of 10 patients with uncontrolled hypertension, increases in blood pressure have been associated with significant clinical events. Zolmitriptan is contraindicated in patients with uncontrolled hypertension. In volunteers, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen at 5 mg. In the headache trials, vital signs were measured only in the small inpatient study and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of zolmitriptan (see CONTRAINDICATIONS). An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT₁ agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General: As with other 5-HT₁ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with ZOMIG Tablets in the pectorum, throat, neck and jaw. Because zolmitriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT₁ agonist are candidates for further evaluation (see WARNINGS). Zolmitriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic function (see CLINICAL PHARMACOLOGY). For a given attack, if a patient does not respond to the first dose of zolmitriptan, the diagnosis of migraine headache should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the value measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylethanolamines: Phenylethanolamines should be informed that ZOMIG-ZMT contain phenylalanine (a component of aspartame). Each 2.5 mg orally disintegrating tablet contains 2.81 mg phenylalanine. Each 5 mg orally disintegrating tablet contains 5.62 mg phenylalanine.

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

ZOMIG-ZMT Orally Disintegrating Tablets: The orally disintegrating tablet is packaged in a blister. Patients should be instructed not to remove the tablet from the blister until just prior to dosing. The blister pack should then be peeled open, and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

Laboratory Tests: No monitoring of specific laboratory tests is recommended.

Drug Interactions: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that 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 should be avoided (see CONTRAINDICATIONS). MAO-A inhibitors increase the systemic exposure of zolmitriptan. Therefore, the use of zolmitriptan in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS). Concomitant use of other 5-HT₁ agonists within 24 hours of ZOMIG treatment is not recommended (see CONTRAINDICATIONS). Following administration of zolmitriptan, the half-life and AUC of zolmitriptan and its active metabolites were approximately doubled (see CLINICAL PHARMACOLOGY). Selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT₁ agonists. If concomitant treatment with zolmitriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug/Laboratory Test Interactions: Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: **Carcinogenesis:** Carcinogenicity studies by oral gavage were carried out in mice and rats at doses up to 400 mg/kg/day. Mice were dosed for 85 weeks (males) and 92 weeks (females). The exposure (plasma AUC of parent drug) at the highest dose level was approximately 800 times that seen in humans after a single 10 mg dose (the maximum recommended total daily dose). There was no effect of zolmitriptan on tumor incidence. Control, low dose and middle dose rats were dosed for 104-105 weeks; the high dose group was sacrificed after 101 weeks (males) and 86 weeks (females) due to excess mortality. Aside from an increase in the incidence of thyroid follicular cell hyperplasia and thyroid follicular cell adenomas seen in male rats receiving 400 mg/kg/day, an exposure approximately 3000 times that seen in humans after dosing with 10 mg, no tumors were noted.

Mutagenesis: Zolmitriptan was mutagenic in an Ames test. In 2 of 5 strains of *S. typhimurium* tested, in the presence of, but not in the absence of, metabolic activation. It was not mutagenic in an *in vitro* mammalian gene cell mutation (CHO/GPRT) assay. Zolmitriptan was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation; it was not clastogenic in an *in vivo* mouse micronucleus assay. It was also not genotoxic in an unscheduled DNA synthesis study.

Impairment of Fertility: Studies of male and female rats administered zolmitriptan prior to and during mating and up to implantation have shown no impairment of fertility at doses up to 400 mg/kg/day. Exposure at this dose was approximately 3000 times exposure at the maximum recommended human dose of 10 mg/day.

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 was associated with embryofetality and fetal abnormalities. When pregnant rats were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400 and 1200 mg/kg/day, there was a dose-related increase in embryofetality which became statistically significant at the high dose. The maternal plasma exposures at these doses were approximately 280, 1100 and 5000 times the exposure in humans receiving the maximum recommended total daily dose of 10 mg. The high dose was maternally toxic, as evidenced by a decreased maternal body weight gain during gestation. In a similar study in rabbits, embryofetality was increased at the maternally toxic doses of 10 and 30 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal malformations (fused sternbrae, rib anomalies) and variations (major blood vessel variations, irregular ossification pattern of ribs) were observed at 30 mg/kg/day. Three mg/kg/day was a no effect dose (equivalent to human exposure at a dose of 10 mg). When female rats were given zolmitriptan during gestation, parturition, and lactation, an increased incidence of hydronephrosis was found in the offspring at the maternally toxic dose of 400 mg/kg/day (1100 times human exposure).

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Nursing Mothers: It is not known whether zolmitriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when zolmitriptan is administered to a nursing woman. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hour and 4 hours higher than plasma levels at 4 hours.

Pediatric Use: Safety and effectiveness of ZOMIG in pediatric patients have not been established. ZOMIG is not recommended for use in patients under 18 years of age. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

Geriatric Use: Although the pharmacokinetic disposition of the drug in the elderly is similar to that seen in younger adults, there is no information about the safety and effectiveness of zolmitriptan in this population because patients over age 65 were excluded from the controlled clinical trials. (see CLINICAL PHARMACOLOGY: Special Populations)

ADVERSE REACTIONS: Serious cardiac events, including myocardial infarction, have occurred following the use of ZOMIG Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported, in association with drugs of this class, have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Among 2,633 patients treated with ZOMIG Tablets in the active and placebo controlled trials, no patients withdrew for reasons related to adverse events, but as patients treated a single headache in these trials, the opportunity for discontinuation was limited. 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 experience. The most common events were paresthesia, asthenia, nausea, dizziness, pain, chest or neck tightness or heaviness, somnolence and warm sensation. Table 1 lists the adverse events that occurred in ≥ 2% of the 2,074 patients in any one of the ZOMIG 1 mg, ZOMIG 2.5 mg or ZOMIG 5 mg Tablets dose groups of the controlled clinical trials. Only events that were more frequent in a ZOMIG Tablets group compared to the placebo groups are included. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Several of the adverse events 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 Experience Incidence in Five Placebo-Controlled Migraine Clinical Trials: Events Reported by ≥ 2% Patients Treated With ZOMIG Tablets

| Adverse Event Type | Placebo (n=401) | ZOMIG 1 mg (n=163) | ZOMIG 2.5 mg (n=498) | ZOMIG 5 mg (n=1012) |
|--|-----------------|--------------------|----------------------|---------------------|
| ATYPICAL SENSATIONS | | | | |
| Hypesthesia | 6% | 12% | 12% | 18% |
| Paresthesia (all types) | 1% | 1% | 1% | 2% |
| Sensation warm/cold | 2% | 5% | 7% | 9% |
| PAIN AND PRESSURE SENSATIONS | | | | |
| Chest-pain/tightness/pressure and/or heaviness | 4% | 6% | 5% | 7% |
| Neck/throat/jaw-pain/tightness/pressure | 7% | 12% | 14% | 22% |
| Heaviness other than chest or neck | 1% | 2% | 3% | 4% |
| Pain-location specified | 3% | 4% | 7% | 10% |
| Other-pressure/tightness/heaviness | 1% | 1% | 2% | 5% |
| DIGESTIVE | | | | |
| Dyspepsia | 1% | 2% | 2% | 3% |
| Dysphagia | 0% | 0% | 0% | 2% |
| Nausea | 4% | 4% | 9% | 6% |
| NEUROLOGICAL | | | | |
| Dizziness | 10% | 11% | 17% | 21% |
| Somnolence | 4% | 6% | 8% | 10% |
| Vertigo | 3% | 5% | 6% | 8% |
| OTHER | | | | |
| Asthenia | 0% | 0% | 0% | 2% |
| Palpitations | 3% | 5% | 3% | 9% |
| Myalgia | 1% | 0% | <1% | 2% |
| Myasthenia | <1% | 1% | 1% | 2% |
| Sweating | <1% | 0% | 1% | 2% |
| | 1% | 0% | 2% | 3% |

ZOMIG is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of the patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of ZOMIG in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used ZOMIG Tablets (n=4,027) and reported an event divided by the total number of patients exposed to ZOMIG Tablets. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare adverse events are those occurring in fewer than 1/1,000 patients.

Atypical sensations: Infrequent was hyperesthesia. **General:** Infrequent were allergy reaction, chills, facial edema, fever, malaise and photosensitization. **Cardiovascular:** Infrequent were arrhythmias, hypertension and syncope. Rare were bradycardia, extrasystoles, postural hypotension, QT prolongation, tachycardia and thrombophlebitis. **Digestive:** Infrequent were increased appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality and thirst. Rare were anorexia, constipation, gastritis, hematemesis, pancreatitis, melena, and ulcer. **Hemic:** Infrequent was acchymosis. Rare were cyanosis, thrombocytopenia, eosinophilia and leukopenia. **Metabolic:** Infrequent was edema. Rare were hyperglycemia and alkaline phosphatase raised. **Musculoskeletal:** Infrequent were back pain, leg cramps and tenosynovitis. Rare were arthritis, asthma, tetany and twitching. **Neurological:** Infrequent were agitation, anxiety, depression, emotional lability and insomnia. Rare were akathisia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertension and irritability. **Respiratory:** Infrequent were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis, and yawn. Rare were apnea and voice alteration. **Skin:** Infrequent were pruritus, rash and urticaria. **Special Senses:** Infrequent were dry eye, eye pain, hyperacusis, ear pain, parosmia, and tinnitus. Rare were diplopia and lacrimation. **Urogenital:** Infrequent were hematuria, cystitis, polyuria, urinary frequency, urinary urgency. Rare were miscarriage and dysmenorrhea.

The adverse experience profile seen with ZOMIG-ZMT Tablets was similar to that seen with ZOMIG Tablets.

Postmarketing Experience with ZOMIG Tablets: The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and non-domestic use of oral zolmitriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of zolmitriptan in their causation cannot be reliably determined.

Cardiovascular: Coronary artery vasospasm; transient myocardial ischemia, angina pectoris, and myocardial infarction. **Digestive:** Very rare gastrointestinal ischemic events including splenic infarction, ischemic colitis, and gastrointestinal infarction or necrosis have been reported; these may present as bloody diarrhea or abdominal pain (see WARNINGS).

Neurological: As with other acute migraine treatments including other 5-HT₁ agonists, there have been rare reports of headache.

General: As with other 5-HT₁ agonists, there have been very rare reports of anaphylaxis or anaphylactoid reactions in patients receiving ZOMIG. There have been rare reports of hypersensitivity reactions, including angioedema.

DRUG ABUSE AND DEPENDENCE: The abuse potential of ZOMIG has not been assessed in clinical trials.

OVERDOSSAGE: There is no experience with clinical overdose. Volunteers receiving single 50 mg oral doses of zolmitriptan commonly experienced sedation. The elimination half-life of ZOMIG is 3 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with ZOMIG should continue for at least 15 hours or while symptoms or signs persist. There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. It is unknown what effect hemodialysis or peritoneal dialysis has on the plasma concentrations of zolmitriptan.

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