

PRODUCT MONOGRAPH

^{Pr} **MYLAN-ZOLMITRIPTAN ODT**

zolmitriptan orally disintegrating tablets

2.5 mg

5-HT₁ Receptor Agonist

MIGRAINE THERAPY

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	orally disintegrating tablet / 2.5 mg	aspartame (a source of phenylalanine), colloidal silicon dioxide, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, orange flavour (artificial)

INDICATIONS AND CLINICAL USE

Adults

Mylan-Zolmitriptan ODT (zolmitriptan) is indicated for the acute treatment of migraine attacks with or without aura.

Mylan-Zolmitriptan ODT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache, which is present in an older, predominantly male population.

Pediatrics (< 12 years of age)

The safety and efficacy of Zolmitriptan have not been studied in children under 12 years of age. Use of the drug in this age group is, therefore, not recommended (see WARNINGS and PRECAUTIONS, Special Populations).

Adolescents (12-17 years of age)

The safety and efficacy of Zolmitriptan have not been established in patients 12-17 years of age. The use of Zolmitriptan in adolescents is, therefore, not recommended (see WARNINGS AND PRECAUTIONS, Special Populations).

Geriatrics (> 65 years of age)

The safety and efficacy of Zolmitriptan in patients over 65 years has not been established and

its use in this age group is not recommended (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

Mylan-Zolmitriptan ODT (zolmitriptan) is contraindicated under the following conditions:

- **in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive Zolmitriptan. Ischemic cardiac syndromes include, but are not restricted to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS AND PRECAUTIONS, Cardiovascular);**
- **in patients with uncontrolled or severe hypertension as Zolmitriptan can give rise to increases in blood pressure (see WARNINGS AND PRECAUTIONS, Hematologic);**
- **within 24 hours of treatment with another 5-HT₁ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide (see DRUG INTERACTIONS);**
- **in patients with hemiplegic, basilar or ophthalmoplegic migraine;**
- **concurrent administration of MAO inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO inhibitor therapy (see DRUG INTERACTIONS);**
- **in patients with hypersensitivity to zolmitriptan or any component of the formulation (for a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING).**

WARNINGS AND PRECAUTIONS

General

Mylan-Zolmitriptan ODT (zolmitriptan) should only be used where a clear diagnosis of migraine has been established.

Psychomotor Effect: Although Zolmitriptan did not interfere with psychomotor performance in healthy volunteers, some patients in clinical trials experienced sedation with Zolmitriptan. Patients should thus be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that Zolmitriptan does not affect them adversely.

Medication Overuse Headache: Overuse of acute migraine treatments has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

Cardiovascular

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:

Zolmitriptan has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT₁ agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of Zolmitriptan. In very rare cases angina pectoris has been reported.

Zolmitriptan should not be given to patients who have 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, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is 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 unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, Zolmitriptan should not be administered (see CONTRAINDICATIONS).

These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events, such as myocardial infarction or coronary ischemia have occurred in patients without evidence of underlying cardiovascular disease.

For patients with risk factors predictive of CAD who are considered to have a satisfactory cardiovascular evaluation, the first dose of Zolmitriptan should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following Zolmitriptan administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

Intermittent long-term users of Zolmitriptan, who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment.

If symptoms consistent with angina occur after the use of Zolmitriptan, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to Zolmitriptan.

As with other 5HT_{1B/1D} agonists, atypical sensations over the precordium have been reported after the administration of zolmitriptan. Where such symptoms are thought to indicate ischemic heart disease, no further doses of zolmitriptan should be given and appropriate evaluation carried out.

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of Zolmitriptan. Because 5-HT₁ agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following Zolmitriptan should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, 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 Zolmitriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Cardiac Events and Fatalities Associated with 5-HT₁ Agonists

As with other triptans, zolmitriptan may cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, 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.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive Zolmitriptan.

Premarketing Experience with Zolmitriptan

Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of Zolmitriptan, no deaths or serious cardiac events were reported.

Postmarketing Experience with Zolmitriptan

Serious cardiovascular events have been reported in association with the use of Zolmitriptan. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of reported cases that were actually caused by Zolmitriptan or to reliably assess causation in individual cases.

Cerebrovascular Events and Fatalities With 5-HT₁ Agonists

Migraineurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, 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 were a consequence of migraine, when they were not. Before treating migraine headaches with Zolmitriptan in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, haemorrhage, TIA).

Special Cardiovascular Pharmacology Studies With Another 5-HT₁ Agonist

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT₁ agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT₁ agonist is not known.

Similar studies have not been done with Zolmitriptan. However, owing to the common pharmacodynamic actions of 5-HT₁ agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Other Vasospasm-Related Events: 5-HT₁ agonists may cause vasospastic reactions other than coronary artery vasospasm. Peripheral vascular ischemia has been reported with 5-HT₁ agonists (see ADVERSE REACTIONS). Very rare reports of splenic infarction and gastrointestinal ischemic events including ischemic colitis, gastrointestinal infarction or necrosis, which may present as bloody diarrhea or abdominal pain, have been received.

Increased Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving other 5-HT₁ agonists with and without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. Isolated reports of chest pain, pulmonary edema, coronary vasospasm, transient cerebral ischemia, angina and subarachnoid hemorrhage have been received (see CONTRAINDICATIONS). In patients with controlled hypertension, Zolmitriptan should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

In pharmacodynamic studies, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen in volunteers with 5 mg Zolmitriptan. In the headache trials, vital signs were measured only in a small, single-centre inpatient study, and no effect on

blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 patients experienced 20 to 80 mm Hg elevations in systolic or diastolic blood pressure after a 10 mg Zolmitriptan dose. Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension who received 5-HT₁ agonists. Zolmitriptan is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS).

Dependence

The abuse potential of Zolmitriptan has not been assessed in clinical trials.

Endocrine and Metabolism

Phenylketonuria: Patients with phenylketonuria should be informed that Zolmitriptan orally disintegrating tablets contain phenylalanine (a component of aspartame). Each orally disintegrating tablet contains 2.8 mg of phenylalanine.

Hepatic

Zolmitriptan should be administered with caution to patients with moderate or severe hepatic impairment, using a dose lower than 2.5 mg (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT₁ agonists such as Zolmitriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, Zolmitriptan should not be used in patients having a history of hypersensitivity to chemically-related 5-HT₁ receptor agonists (see Adverse Events in PRECAUTIONS ADVERSE REACTIONS).

Neurologic

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT₁ agonists for severe headache that were subsequently shown to have been secondary to an evolving neurological lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of Zolmitriptan.

Seizures: Caution should be observed if Zolmitriptan is to be used in patients with a history of epilepsy or structural brain lesions, which lower the convulsion threshold.

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors

(SNRIs) and triptans. If concomitant treatment with Zolmitriptan and SSRIs (e.g., fluoxetine, paroxetine, sertraline) or SNRIs (e.g., venlafaxine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. 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) (see DRUG INTERACTIONS).

Ophthalmologic

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 10 mg/kg of radiolabelled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the values 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, it 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. No systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, however, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Preclinical Toxicology

Carcinogenicity: Carcinogenicity studies by oral gavage were carried out in rats and mice at doses up to 400 mg/kg/day. In mice the total exposure at the highest dose level was approximately 800 times that seen after a single 10 mg dose in humans and there was no effect on tumour type or incidence. In male rats at this dose level, where total exposure was approximately 3000 times that seen after a single 10 mg dose in humans, there was an increase in the incidence of thyroid follicular hyperplasia and benign adenomata. This has been shown to be due to an increase in thyroxine clearance caused by zolmitriptan at this dose level with a resultant chronic stimulation of the thyroid. There was no effect on tumour profile at the dose level of 100 mg/kg/day that gave an exposure multiple of approximately 800.

Mutagenicity: Zolmitriptan was mutagenic in an Ames test, in 2 of 5 strains of *Salmonella 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/HGPRT) assay. Zolmitriptan was clastogenic in an in vitro human lymphocyte assay both in the absence of and the presence of metabolic activation. Zolmitriptan was not clastogenic in an in vivo mouse micronucleus assay. Zolmitriptan was not genotoxic in an unscheduled DNA synthesis study.

Special Populations

Pregnant Women: Reproductive studies in male and female rats, at dose levels limited by toxicity, revealed no effect on fertility or reproduction.

Reproduction studies in rats and rabbits dosed during the period of organogenesis have been performed at levels limited by maternal toxicity. In rats dosed orally by gavage at 1200 mg/kg/day, giving a total exposure 3000 - 5000 times that seen following a single 10 mg dose in humans, there was a slight increase in early resorptions but no effect on fetal malformations. At a dose of 400 mg/kg/day in rats, an exposure multiple of approximately

1100, there were no effects of any kind on the fetus. The maximum achieved dose in rabbits was 30 mg/kg/day that gave a total exposure 30 - 40 times that seen following a single 10 mg dose in humans and there were no fetal effects.

The safety of Zolmitriptan for use during human pregnancy has not been established. Zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: It is not known whether zolmitriptan and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when considering the administration of Zolmitriptan to nursing women. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

Pediatrics (<12 years of age): The safety and efficacy of Zolmitriptan have not been studied in children under 12 years of age. Use of the drug in this age group is, therefore, not recommended.

Adolescents (12-17 years of age): Systemic exposure to the parent compound does not differ significantly between adolescents and adults, however exposure to the active metabolite is greater in adolescents (see ACTION AND CLINICAL PHARMACOLOGY). The safety and efficacy of Zolmitriptan have not been established in patients 12-17 years of age. The use of Zolmitriptan in adolescents is, therefore, not recommended.

In a single randomized placebo-controlled study of 696 adolescent migraineurs (aged 12-17 years), the efficacy of Zolmitriptan tablets (2.5, 5 and 10 mg) was not established (see ADVERSE REACTIONS, Special Populations).

Geriatrics (> 65 years of age): The safety and efficacy of Zolmitriptan have not been studied in individuals over 65 years of age. The risk of adverse reactions to this drug may be greater in elderly patients as they are more likely to have decreased hepatic function, be at higher risk for CAD, and experience blood pressure increases that may be more pronounced. Clinical studies did not include patients over 65 year of age. Its use in this age group is, therefore, not recommended.

Special Disease Conditions:

Zolmitriptan should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic function (see WARNINGS AND PRECAUTIONS, Hepatic).

Monitoring and Laboratory Tests

Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

ADVERSE REACTION

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT₁ agonists. These events are extremely rare and most have been reported in

patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, angina pectoris, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, General).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Frequencies of adverse events are reported as follows:

Very common ($\geq 10\%$)

Common ($\geq 1\% - < 10\%$)

Uncommon ($\geq 0.1\% - < 1\%$)

Rare ($\geq 0.01\% - < 0.1\%$)

Very Rare ($< 0.01\%$)

Experience in Controlled Clinical Trials with Zolmitriptan

Typical 5-HT₁ Agonist Adverse Reactions: As with other 5-HT₁ agonists, Zolmitriptan has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb. In very rare cases, as with other 5-HT₁ agonists, angina pectoris and myocardial infarction have been reported.

Transient increases in systemic blood pressure, have been reported in patients, with and without a history of hypertension. Very rarely these increases in blood pressure have been associated with significant clinical events. Isolated reports of chest pain, pulmonary edema, coronary vasospasm, transient cerebral ischemia, angina and subarachnoid hemorrhage have been received (see WARNINGS AND PRECAUTIONS, Cardiovascular, Increased Blood Pressure).

There have been rare reports of hypersensitivity reactions including urticaria and angioedema (see WARNINGS AND PRECAUTIONS, Immune).

EXPERIENCE IN CONTROLLED CLINICAL TRIALS WITH ZOLMITRIPTAN ODT

Acute Safety: In an international, placebo-controlled, double-blind trial to evaluate the efficacy and tolerability of Zolmitriptan ODT 2.5 mg in the acute treatment of adult patients with migraine, 231 patients received at least one dose of Zolmitriptan ODT. Most of

the adverse events were of mild or moderate intensity, and no patients withdrew from the trial because of adverse events. The types of adverse events reported were consistent with known effects of this class of compound (5-HT_{1B/1D}) and were similar to those reported with the Zolmitriptan conventional tablet. The most frequently reported adverse events (>2%) for Zolmitriptan ODT 2.5 mg versus placebo, respectively, were asthenia (3% vs. 1%), tightness (3% vs. <1%), somnolence (3% vs. 2%), dizziness (3% vs. 1%), paresthesia (3% vs. 2%), hyperesthesia (2% vs. 0%), pharyngitis (2% vs. 0%), and nausea (2% vs. 1%).

Overall Results of Clinical Trials

In a pool of 51 placebo-controlled and open labelled studies the above adverse events were reported at the described frequencies, with the exception of the following adverse events which were reported at a greater frequency. In total 17,301 patients with migraine were treated with Zolmitriptan conventional tablets, Zolmitriptan oral disintegrating tablets and Zolmitriptan nasal spray. Events are classified within body system categories and enumerated in order of decreasing frequency.

Cardiac Disorders: Uncommon was tachycardia.

Gastrointestinal Disorders: Common was dysphagia.

Nervous System Disorders: Common was headache.

Vascular Disorders: Uncommon was transient increases in systemic blood pressure.

Sensations of heaviness, tightness, pain or pressure in the throat, neck, limbs or chest were common.

Adverse Drug Reactions in Special Population

Adolescents (12-17 years of age)

Table 1 lists the adverse events observed in a single randomized placebo-controlled study of 696 adolescent migraineurs aged 12-17 years (see WARNINGS AND PRECAUTIONS, Special Populations).

Table 1 Adverse events in a single placebo-controlled adolescent study, reported by $\geq 1\%$ of patients treated with Zolmitriptan

Body System and Adverse Event (COSTART term)	Percentage of Patients			
	Placebo (N=176)	2.5 mg (N=171)	5 mg (N=174)	10 mg (N=178)
Cardiovascular				
Vasodilatation	0.6	0	2.9	3.9
Palpitation	0	0	1.1	0
Whole Body				
Tightness	1.1	2.9	5.7	11.2
Asthenia	1.1	1.8	1.1	5.1
Pain	0	1.8	1.7	5.1
Neck Pain	0	0.6	1.7	3.4
Abdominal Pain	0.6	1.2	0	1.7
Headache	0	1.2	2.9	1.1
Malaise	0	0	2.3	0.6
Pressure	0	1.8	0.6	0.6
Stiffness	0	0	0.6	2.8
Heaviness	1.1	0.6	0	1.1
Digestive				
Nausea	1.1	5.8	2.9	7.9
Vomiting	1.1	0.6	1.7	4.5
Dry Mouth	0.6	1.8	1.1	1.1
Nervous System				
Dizziness	2.3	4.7	4.6	9.0
Paresthesia	0	1.8	4.6	6.2
Somnolence	1.7	1.2	1.7	2.8
Hypertonia	0	0.6	1.7	1.1
Internasal Paresthesia	0	2.3	0.6	0
Tremor	0	0	0	1.7
Hyperesthesia	0	0	0	1.1
Respiratory System				
Pharyngitis	0.6	2.9	2.3	1.7
Dyspnea	0.6	0	1.1	0.6
Musculoskeletal				
Myalgia	0	0	1.1	0.6
Skin and Appendages				
Sweating	0	0	0	1.7
Special Senses				
Eye Pain	0	0.6	1.1	0.6
Amblyopia	0	0	0	1.1

Post-Market Adverse Drug Reactions

In addition to the adverse experiences reported during clinical testing of Zolmitriptan, the following adverse experiences have been reported in patients receiving marketed

Zolmitriptan from worldwide use since approval. There are insufficient data to support an estimate of their incidence or to establish causality.

Serious adverse events have occurred during post-marketing surveillance following the use of Zolmitriptan oral tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, angina pectoris and myocardial infarction (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Post-market reports show that dysphagia has been reported commonly when using Zolmitriptan.

As with other 5-HT_{1B/1D} agonists, there have been very rare reports of anaphylaxis or anaphylactoid reactions and gastrointestinal ischemic events including ischemic colitis, gastrointestinal infarction, splenic infarction, or necrosis, which may present as bloody diarrhea or abdominal pain.

Post-marketing experience with other triptans include a limited number of reports that describe pediatric (under 12 years of age) and adolescent (12 - 17 years of age) patients who have experienced clinically serious adverse events that are similar in nature to those reported as rare occurrences in adults.

DRUG INTERACTIONS

Drug-Drug Interactions

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, the use of ergot-containing or ergot-type medications (like dihydroergotamine or methysergide and zolmitriptan) within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

Other 5-HT₁ Agonists: The administration of Zolmitriptan with other 5-HT₁ agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT₁ agonists, use of these drugs within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

All drug interaction studies with drugs listed below were performed in healthy volunteers using a single 10 mg dose of Zolmitriptan and a single dose of the other drug, except where otherwise noted.

MAO Inhibitors: In a limited number of subjects, following one week administration of 150 mg b.i.d. moclobemide, a specific MAO-A inhibitor, there was an increase of approximately 26% in both AUC and C_{max} for zolmitriptan and a 3-fold increase in the AUC and C_{max} of the active N-desmethyl metabolite. Administration of selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for one week, had no effect on the pharmacokinetic parameters of zolmitriptan and the active N-desmethyl metabolite. The specificity of selegiline diminishes

with higher doses and varies between patients. Therefore, co-administration of zolmitriptan in patients taking MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

Cimetidine and other 1A2 Inhibitors: Following administration of cimetidine, a general P450 inhibitor, the half life and AUC of zolmitriptan and its active metabolite were approximately doubled. Patients taking cimetidine should not exceed a dose of 5 mg Zolmitriptan in any 24 hour period. Based on the overall interaction profile, an interaction with specific inhibitors of CYP 1A2 cannot be excluded. Therefore, the same dose reduction is recommended with compounds of this type, such as fluvoxamine and the quinolones (e.g., ciprofloxacin). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Oral Contraceptives: Retrospective analysis of pharmacokinetic data across studies indicated that mean plasma concentrations of zolmitriptan were generally greater in females taking oral contraceptives compared to those not taking oral contraceptives. Mean C_{max} and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and T_{max} was delayed by 30 minutes in females taking oral contraceptives. The effect of Zolmitriptan on the pharmacokinetics of oral contraceptives has not been studied.

Propranolol: Propranolol, at a dose of 160 mg/day for 1 week increased the C_{max} and AUC of zolmitriptan by 1.5-fold. C_{max} and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors: Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see WARNINGS AND PRECAUTIONS).

The pharmacokinetics and effects of Zolmitriptan on blood pressure were unaffected by 4-week pre-treatment with oral fluoxetine (20 mg/day). The effects of zolmitriptan on fluoxetine metabolism were not assessed.

Acetaminophen: After concurrent administration of single 10 mg doses of Zolmitriptan and 1 g acetaminophen, there was no significant effect on the pharmacokinetics of Zolmitriptan. Zolmitriptan reduced the AUC and C_{max} of acetaminophen by 11% and 31% respectively and delayed the T_{max} of acetaminophen by 1 hour.

Metoclopramide: Metoclopramide (single 10 mg dose) had no effect on the pharmacokinetics of Zolmitriptan or its metabolites.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Zolmitriptan is recommended only for the acute treatment of migraine attacks. Zolmitriptan should not be used prophylactically.

The recommended adult starting dose for Zolmitriptan is 2.5 mg (see individual dosage forms

under DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

If the headache returns, the dose may be repeated after 2 hours. A dose should not be repeated, regardless of dosage form, within 2 hours. A total cumulative dose of 10 mg should not be exceeded in any 24 hour period.

Controlled trials have not established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating more than 3 migraine headaches with Zolmitriptan in a one month period remains to be established.

Hepatic Impairment: Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and significant elevation in blood pressure was observed in some patients. Use of a low dose (<2.5 mg) with blood pressure monitoring is recommended (see ACTION AND CLINICAL PHARMACOLOGY and WARNINGS AND PRECAUTIONS, Hepatic).

Hypertension: Zolmitriptan should not be used in patients with uncontrolled or severe hypertension. Patients with mild to moderate hypertension should be treated cautiously at the lowest effective dose.

Cimetidine and other 1A2 Inhibitors: Patients taking cimetidine and other 1A2 inhibitors should not exceed a dose of 5 mg Zolmitriptan in any 24 hour period (see DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

Adults: The minimal effective single adult dose of Zolmitriptan is 1 mg. The recommended single dose is 2.5 mg. **The Zolmitriptan ODT 2.5 mg orally disintegrating tablet cannot be broken in half to approximate a 1 mg dose.**

The Zolmitriptan orally disintegrating tablet rapidly dissolves when placed on the tongue and is swallowed with the patient's saliva. Zolmitriptan ODT can be taken when water is not available thus allowing early administration of treatment for a migraine attack. This formulation may also be beneficial for patients who suffer from nausea and are unable to drink during a migraine attack, or for patients who do not like swallowing conventional tablets.

Administration

The tablet should be placed on the tongue, where it will dissolve with the saliva. Water is not needed for the disintegrating tablet.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

There is no experience with clinical overdose. Volunteers receiving single 50 mg oral doses of Zolmitriptan commonly experienced sedation.

The elimination half-life of zolmitriptan is 2.5 - 3 hours (see ACTION AND CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with Zolmitriptan 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 serum concentrations of zolmitriptan.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics

Zolmitriptan is a selective 5-hydroxytryptamine₁ (5-HT_{1B/1D}) receptor agonist. It exhibits a high affinity at human recombinant 5-HT_{1B} and 5-HT_{1D} receptors and modest affinity for 5-HT_{1A} receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT₂, 5-HT₃, 5-HT₄, alpha₁, alpha₂, or beta₁, -adrenergic; H₁, H₂, histaminic; muscarinic; dopamine₁, or dopamine₂, receptors. The N-desmethyl metabolite of zolmitriptan also has high affinity for 5-HT_{1B/1D} and modest affinity for 5-HT_{1A} receptors.

It has been proposed that symptoms associated with migraine headaches arise from the activation of the trigemino-vascular system, which results in local cranial vasodilation and neurogenic inflammation involving the antidromic release of sensory neuropeptides [Vasoactive Intestinal Peptide (VIP), Substance P and calcitonin gene related peptide (CGRP)]. The therapeutic activity of zolmitriptan for the treatment of migraine headache is thought to be attributable to its agonist effects at 5-HT_{1B/1D} receptors on the intracranial blood vessels, including the arterio-venous anastomoses, and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

Pharmacokinetics

Absorption and Bioavailability: In man, zolmitriptan is rapidly and well absorbed (at least 64%) after oral administration with peak plasma concentrations occurring in 2 hours. The mean absolute bioavailability of the parent compound is approximately 40%. Food has no significant effect on the bioavailability of zolmitriptan.

During a moderate to severe migraine attack in male and female patients, mean AUC_{0-4} and C_{max} for zolmitriptan 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.

Plasma Kinetics and Disposition: When given as a single dose to healthy volunteers, zolmitriptan displayed linear kinetics over the dose range of 2.5 to 50 mg.

Distribution: The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan over the concentration range of 10 - 1000 ng/L is 25%.

There is no evidence of accumulation on multiple dosing with zolmitriptan up to doses of 10 mg.

Metabolism and Excretion: Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. The enzymes responsible for the metabolism of zolmitriptan remain to be fully characterized. The mean elimination half-life of zolmitriptan is approximately 2.5 to 3 hours. Mean total plasma clearance of zolmitriptan 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.

In a study in which radiolabelled zolmitriptan was orally administered to healthy volunteers, 64% and 30% of the administered ^{14}C -zolmitriptan dose was excreted in the urine and feces, respectively. About 8% of the dose was recovered in the urine as unchanged zolmitriptan. The indole acetic acid and N-oxide metabolites, which are inactive, accounted for 31% and 7% of the dose, respectively, while the active N-desmethyl metabolite accounted for 4% of the dose.

Conversion of zolmitriptan to the active N-desmethyl metabolite occurs such that metabolite concentrations are approximately two thirds that of zolmitriptan. Because the 5-HT_{1B/1D} potency of the N-desmethyl metabolite is 2 to 6 times that of the parent, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration. The half-life of the active N-desmethyl metabolite is 3 hours and the T_{max} is approximately 2 to 3 hours.

Special Populations and Conditions

Adolescents (12 - 17 years of age): In a single dose pharmacokinetic study of 5 mg zolmitriptan, systemic exposure to the parent compound was not found to differ significantly between adolescents and adults. However, plasma levels of the active metabolite were significantly greater (40 - 50%) in adolescents than adults.

Geriatrics (>65 years of age): Zolmitriptan pharmacokinetics in healthy elderly non-migraineur (non-migraine sufferers) volunteers (age 65 - 76) were similar to those in younger non-migraineur volunteers (age 18 - 39).

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

Race: The effect of race on the pharmacokinetics of zolmitriptan has not been systematically evaluated. Retrospective analysis of pharmacokinetic data between Japanese and Caucasian subjects revealed no significant differences.

Hepatic Insufficiency: A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and C_{max} were increased by 94% and 50% respectively in patients with moderate liver disease and by 226% and 47% in patients with severe liver disease compared with healthy volunteers. Exposure to the metabolites, including the active N-desmethyl metabolite, was decreased. For the N-desmethyl metabolite, AUC and C_{max} were reduced by 33% and 44% in patients with moderate liver disease and by 82% and 90% in patients with severe liver disease.

Zolmitriptan tablets should be administered with caution in subjects with liver disease generally using doses less than 2.5 mg (see WARNINGS AND PRECAUTIONS).

The plasma half-life ($t_{1/2}$) of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding $t_{1/2}$ values for the N-desmethyl metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively.

Seven out of 27 patients with hepatic impairment (4 with moderate and 3 with severe liver disease) experienced 20 to 80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10 mg dose. Zolmitriptan should be administered with caution in subjects with moderate or severe liver disease (see WARNINGS AND PRECAUTIONS, Hepatic and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Following oral dosing in patients with severe renal impairment ($Cl_{Cr} \geq 5 - \leq 25$ mL/min), clearance of zolmitriptan was reduced by 25% compared to normal ($Cl_{Cr} \geq 70$ mL/min). There was no significant change observed in the clearance of zolmitriptan in patients with moderate renal impairment ($Cl_{Cr} \geq 26 - \leq 50$ mL/min).

Hypertension: No differences in the pharmacokinetics of zolmitriptan were noted in mild to moderate hypertensive volunteers compared to normotensive controls. In this study involving a limited number of patients, small dose-dependent increases in systolic and diastolic blood pressure (approximately 3 mm Hg) did not differ between mild/moderate hypertensives and normotensive controls.

STORAGE AND STABILITY

Mylan-Zolmitriptan ODT should be stored at room temperature between 15 and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

Zolmitriptan orally disintegrating 2.5 mg tablets are white to off-white, round, bevelled edge, debossed with “M” on one side of the tablet and “ZT1” on the other side. Available in blister packs of 6 tablets.

Composition

Mylan-Zolmitriptan ODT

Nonmedicinal ingredients: aspartame (a source of phenylalanine), colloidal silicon dioxide, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, orange flavour (artificial).

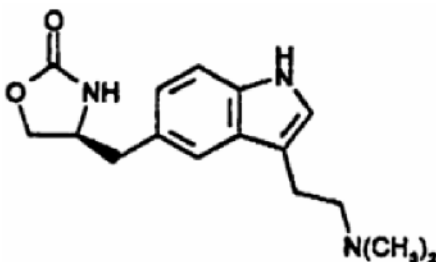
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	Zolmitriptan
Chemical Name:	(S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone
Molecular Formula and Molecular Mass:	C ₁₆ H ₂₁ N ₃ O ₂ and 287.36 g/mol

Structural Formula:



Physiochemical Properties:	White to cream colour powder
Solubility:	slightly soluble in water (1.0 –1.1 mg/mL at 25 °C), 0.1M hydrochloric acid (30.3 mg/mL at 25 °C)
pH and pKa values:	
pH (1% aqueous suspension):	~10.62
pKa:	8.9
Partition co-efficient:	octanol-1-ol/water partition log KD=-1.0
Melting point:	135 – 140°C
UV absorption maxima:	~225 nm

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, two-period, two-treatment, crossover, single dose comparative evaluation of relative oral bioavailability study of ^{Pr} Mylan-Zolmitriptan ODT 2.5 mg (Mylan Pharmaceuticals ULC) and ^{Pr} ZOMIG RAPIMELT[®] (Zolmitriptan) 2.5 mg (AstraZeneca Canada Inc.) was conducted in twenty four healthy adult male subjects under fasting conditions.

A summary of the results is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Zolmitriptan (1 x 2.5 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				

Parameter	Test*	Reference [†]	% Ratio of Geometric Means	Confidence Interval (90%)
AUC _T (ng•h/mL)	20.05 21.46 (36.06)	21.31 22.74 (36.99)	94.08	87.85 -100.76
AUC _I (ng•h/mL)	21.33 22.85 (36.63)	22.70 24.22 (36.95)	93.94	87.83 -100.48
AUC _{0-2h} (ng•h/mL)	4.37 4.72 (43.03)	5.35 5.71 (38.30)	81.78	72.11 - 92.76
C _{max} (ng/mL)	4.27 4.58 (39.96)	4.56 4.77 (30.77)	93.73	85.55 -102.69
T _{max} [§] (h)	1.88 (0.50-5.00)	1.75 (0.50-6.00)		
T _{1/2} ^ε (h)	2.43 (22.52)	2.68 (31.00)		

* ^{Pr} Mylan- Zolmitriptan ODT 2.5 mg Orally Disintegrating Tablets, Mylan Pharmaceuticals ULC.

[†] ^{Pr} ZOMIG RAPIMELT[®] (Zolmitriptan) 2.5 mg Orally Disintegrating Tablets, AstraZeneca Canada Inc. (purchased in Canada).

[§] Expressed as the median (range) only.

^ε Expressed as the arithmetic mean (CV %) only.

The efficacy of Zolmitriptan was not affected by the presence of aura and was independent of headache duration pre-treatment, relationship to menses, gender, age or weight of the patient, pre-treatment nausea and concomitant use of common migraine prophylactic drugs.

ZOLMITRIPTAN ODT

The efficacy and tolerability of Zolmitriptan ODT 2.5 mg tablets in the acute treatment of adult patients with migraine was evaluated in an international, randomized, placebo-controlled, double-blind trial. A total of 471 patients [87% female; 97% Caucasian; mean age 41 years (18 - 62)] were exposed to trial medication, 231 were randomized to zolmitriptan and 240 to placebo. Each patient was instructed to treat a single migraine of moderate or severe intensity with double-blind medication. If sufficient relief was not obtained 2 hours after the first dose, a second dose or escape medication could be taken. Headache response, defined as a reduction of headache pain from moderate or severe at the time of treatment to mild or none at assessment, was evaluated at 0.5, 1, 2, and 4 hours after the first dose. The primary endpoint was headache response at 2 hours.

When compared to the placebo treatment group, a statistically significant greater proportion of the Zolmitriptan ODT group experienced a headache response within 2 hours of initial dosing (primary endpoint, see Table 2). Patients treating with Zolmitriptan ODT also had statistically significant headache response relative to placebo at 0.5, 1 and 4 hours post-dose.

Table 2 Percentage of Patients with Headache Response* at 2 Hours Post-Dose by Treatment Group (ITT Population)

Zolmitriptan ODT Group		Placebo Treatment Group		Statistical Comparison of Zolmitriptan ODT versus Placebo
N	Headache Response N (%) ^a	N	Headache Response N (%) ^a	p-value
220	138 (63)	236	53 (22)	<0.0001

^a Percentages are based upon the total number of patients in the ITT population for which data were available at 2 hours following a single attack.

ITT Intent to treat population – the subset of randomized patients who received trial medication and who received at least one efficacy evaluation.

* Headache response is the diminution of headache pain from moderate or severe at the time of treatment to mild or none at the assessment.

Assessment of the number of patients who were pain-free after treating a migraine attack revealed that 27% of patients treating with Zolmitriptan ODT were pain free at 2 hours compared to 7% treating with placebo (p<0.001). The number of patients pain-free through 24 hours after treatment with a single dose of trial medication was also greater in the Zolmitriptan ODT (23%) than in the placebo (7%) group.

The median time to second treatment (second dose or escape medication) was more than twice as long in the Zolmitriptan ODT treatment group relative to placebo, 5 hours and 45 minutes versus 2 hours and 10 minutes.

The efficacy and tolerability of Zolmitriptan ODT 2.5 mg tablets in the acute treatment of adult patients with migraine was also evaluated in a second randomized, multi-centre, parallel-group, placebo-controlled, double-blind trial. A total of 565 patients [85% female; 85% Caucasian; mean age 41 years (18 - 65)] were randomized to zolmitriptan (n=281) or placebo (n=284) and consumed

at least 1 dose of study medication. Each patient was instructed to treat two separate migraine headaches of mild, moderate, or severe intensity with double-blind medication. For each migraine, if sufficient relief was not obtained 2 hours after the first dose, a second dose or escape medication could be taken. The primary endpoint was the overall pain-free response rate over two migraine attacks at 2 hours after dosing. Pain-free response was defined as an improvement in headache pain from mild, moderate or severe to no pain at assessment (2 hours after dosing). When compared to the placebo treatment group, a statistically significant proportion of the Zolmitriptan ODT group experienced a pain-free response within 2 hours of dosing (see Table 3).

Table 3 Pain Free Response* at 2 Hours Post-Dose by Treatment Group (ITT Population)

Migraine Attack	Zolmitriptan ODT Group		Placebo Treatment Group		Statistical Comparison of Zolmitriptan ODT versus Placebo
	N	Pain-free Response N (%) ^a	N	Pain-free Response N (%) ^a	p-value
Total ^b	526	211 (40)	524	104 (20)	<0.001
1 st attack ^c	278	114 (41)	282	55 (20)	Not analyzed ^c
2 nd attack ^c	248	97 (39)	242	49 (20)	Not analyzed ^c

a Percentages are based upon the total number of attacks (N) in the ITT population for which data were available at 2 hours.

b Primary efficacy endpoint was the overall pain-free response rate over 2 migraine attacks.

c The analysis of the first and second attacks individually was performed as a secondary variable and not statistically analysed.

ITT Intent to treat population – the subset of randomized patients who received trial medication and who received at least one efficacy evaluation.

* Pain-free response is the improvement in migraine headache pain intensity from mild, moderate or severe to no pain at the assessment.

Remedication rates were higher in the placebo group for both attacks, compared to the Zolmitriptan ODT treatment group and time to remedication was statistically significantly shorter in the placebo group (p<0.001).

Patients treating migraines with Zolmitriptan ODT were more likely to experience relief of nausea, photophobia, and phonophobia relative to placebo at the primary endpoint of 2 hours.

DETAILED PHARMACOLOGY

Pharmacodynamics

in vitro: Receptor specificity studies using radioligand binding assays and isolated intact tissue assays have shown that zolmitriptan is a selective 5-HT₁ partial receptor agonist which exhibits a high affinity at human recombinant 5-HT_{1D} (pKi = 9.2) and 5-HT_{1B} (pKi = 8.2) receptors and modest affinity for 5-HT_{1A} receptors (pKi = 7.0). Zolmitriptan had no significant affinity or

pharmacological activity at 5-HT₂, 5-HT₃, 5-HT₄, alpha₁, alpha₂, or beta₁, -adrenergic; H₁, H₂, histaminic; muscarinic; dopamine₁, or dopamine₂, receptors.

in vivo: In anesthetized animals, zolmitriptan (0.3 - 100 µg/kg i.v.) caused dose-related and sustained reductions in carotid arterial blood flow and conductance (ED₅₀ for dogs: 2.9 µg/kg; for cats: 1.1 µg/kg). This reflected a constriction of cranial arteriovenous anastomoses (AVA), with a very minor contribution from the extracranial circulation. No equivalent reductions occurred in cerebral blood flow and conductance in these animals. At doses of 30 µg/kg and 100 µg/kg, i.v., zolmitriptan inhibited trigeminal ganglion electrically stimulated release of calcitonin gene related peptide in anesthetized cats. The effect of trigeminal ganglion stimulation on vasoactive intestinal peptide was also attenuated, in this animal model, by 100 µg/kg zolmitriptan administered i.v. Over a dose range of 3 - 30 µg/kg (i.v.), zolmitriptan caused a dose-related inhibition of neurogenic plasma protein extravasation into the ipsilateral dura mater following electrical stimulation of the trigeminal ganglion.

At higher doses (>100 µg/kg), zolmitriptan produced some systemic cardiovascular effects (notably inconsistent and poorly dose-related increases in blood pressure and heart rate in conscious animals). These systemic effects were species-specific and modified by anesthesia. Apart from its selective vasoconstrictor action in vascular beds supplied by the carotid artery, zolmitriptan had little or no effect at doses up to 1 mg/kg in other major systemic vascular beds, including the coronary and pulmonary circulations. Only in dog renal vasculature was zolmitriptan found also to cause dose-related vasoconstrictor responses.

Zolmitriptan elicited some central nervous system and behavioural effects at high doses (1 or 2 mg/kg), but the severity of these effects were species-specific.

Zolmitriptan exhibited no general autonomic effects, but at low doses (3 -100 µg/kg i.v.) had a selective effect on the sympathetic innervation to the carotid vasculature consistent with agonist activity at pre-junctional inhibitory 5-HT_{1D}-like receptors.

Zolmitriptan did not cause any important respiratory effects except at high doses (>1 mg/kg). However, at these doses other central nervous system and behavioural effects may contribute.

Zolmitriptan had no effects on gastrointestinal function except at very high doses (30 mg/kg, p.o.). Likewise, the drug was without important effect on renal function and barbiturate sleeping times.

The metabolism of zolmitriptan in man results in the formation of a pharmacologically active N-demethylated derivative (see Part I: ACTION AND CLINICAL PHARMACOLOGY). This metabolite exhibited the same pharmacological specificity as the parent molecule, but was 2 to 6 times more potent at 5-HT_{1D} receptors. The cardiovascular profile of the metabolite was qualitatively the same as that of zolmitriptan.

Pharmacokinetics

Absorption of radiolabelled drug-related material was rapid following oral administration of zolmitriptan to mice, rats, rabbits and dogs with C_{max} occurring within 1 hour of dosing. In the rat, C_{max} was reached at 0.5 hour with a secondary peak at 3 hours after dosing. This occurred in both males and females. A second peak was not detected following intravenous administration

therefore it is likely a result of continuing absorption lower in the gastrointestinal tract. Oral bioavailabilities of 50% in mice (10 mg/kg), 41% in rats (10 mg/kg), 25% in rabbits (10 mg/kg) and 79% in dogs (2 mg/kg) suggest significant first pass metabolism, particularly in the rabbit. In man, absorption is at least 64% after oral administration, with a mean absolute bioavailability of the parent compound of approximately 40%.

Preclinical studies in the rat, rabbit, and Cynomolgus monkey have shown that the disposition of zolmitriptan is similar following nasal and oral administration. Total recoveries of radioactivity in urine and feces following oral administration of zolmitriptan were 65% and 30% of the administered dose, respectively. About 8% of the oral dose was recovered in the urine as unchanged zolmitriptan. The 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. In addition, preclinical studies in the rat and rabbit have shown that the disposition of zolmitriptan is similar following single and multiple nasal and oral administration.

In all animal species elimination from plasma was rapid with $t_{1/2}$ of 1 to 2 hours. There were no apparent differences due to gender or route of administration. The $t_{1/2}$ in man was 2.5 to 3 hours.

In the toxicity studies, exposure was generally linear with increasing dose. The pharmacokinetics following multiple dosing were similar to those observed after single dose administration. However, in the rat, exposures to zolmitriptan and the indole acetic acid metabolite increased time-dependently for the first 52 weeks of chronic dosing and subsequently decreased at 78 and 104 weeks. In the teratology studies, the exposure to zolmitriptan and the metabolites were not significantly different between pregnant and non-pregnant rats. However, in female rabbits, there appeared to be an increase in exposure over the dosing period. After chronic dosing to the dog, there was a slight variation in exposure to the N-oxide metabolite that increased relative to zolmitriptan.

The tissue distribution of zolmitriptan was investigated in the male rat using both albino and pigmented strains. The highest levels of distribution were found in the liver, kidney and glandular tissues. Minimal crossing of the blood-brain barrier was observed. The radioactive drug-related material was rapidly eliminated. Levels of radioactivity in the tissue of albino and pigmented rats were comparable at all time points, apart from the eye which had higher levels in the pigmented rat, indicating an association with melanin. In a study with pigmented rats, in which animals were given a single oral dose of 10 mg/kg radiolabelled zolmitriptan, radioactivity was notable in the eye up to 7 days (last time point examined) after drug administration and was still 75% of the value measured at the 4 hour time point post-dose.

Studies in pregnant rats and rabbits demonstrated exposure to the placenta and fetus while nursing rats had milk levels of radioactivity equivalent to plasma at 1 hour post dose and four times higher than plasma at 4 hours post dose.

Metabolite patterns of zolmitriptan are qualitatively similar in all animal species and man. Zolmitriptan was the major component of all urinary and faecal samples from mice, rats and rabbits while the indole acetic acid metabolite formed the major component in dogs and man.

Drug-related material was rapidly excreted in all species. Urine was the primary route of excretion, >50% of the dose, except after oral dosing to rodents that accounted for 30-35% of the dose. Biliary excretion in the rat was minimal (<4%) despite the excretion of 22% of an intravenous dose, indicating direct secretion into the gut.

TOXICOLOGY

Acute Toxicity

In oral acute studies in mice the approximate lethal dose of zolmitriptan was 1000 mg/kg and in rats the approximate lethal dose was between 1000 and 1500 mg/kg. Although exposure was not measured, the approximate oral lethal dose of zolmitriptan in rodents is about 20,000 times the usual human dose of 2.5 mg. The approximate lethal dose was 50 - 100 mg/kg following intravenous administration. Animals were found dead without premonitory signs.

Long-Term Toxicity

Repeated dose studies in rats (up to 1000 mg/kg/day) and dogs (up to 100 mg/kg/day) have revealed little toxicity other than clinical signs, which are associated with an excess of the pharmacological action of this class of compound. Dose limiting factors were: in rats, sporadic deaths at the highest dose level, in dogs, clinical and behavioural changes, believed to be due to perturbations of 5-HT_{1D} regulated central nervous system pathways. Details of each study are provided in Table 4.

Table 4 Long-Term Toxicity

TYPE	STUDY	SPECIES	No/GROUP M/F	DOSE mg/kg/day	FINDINGS
Oral/Intravenous Administration					
One Month Toxicity	Daily dosing oral	Wistar rat	15/15	0, 100, 400, 1600/1000 from day 10	Excessive mortality at 1600 mg. Very slight urothelial hyperplasia in a few 1600/1000 mg animals. Pink extremities all dose levels. 3 deaths at 400 mg. Slight increase in thyroid weight at 1600/1000 mg.
	Daily dosing oral	Beagle dog	3/3 Groups 2+3 5/5 Groups 1+4	0, 5, 25, 100	No toxic effect level 100 mg/kg/day. Clinical signs at all dose levels which reduced with continued dosing. One 100 mg animal collapsed on two occasions but survived. Withdrawal signs: mydriasis, photophobia.
One Month Toxicity	Daily dosing intravenous	Wistar rat	15/15	0, 0.5, 2, 10	No toxic effect level 25 mg/kg/day. Expected clinical signs at 2 and 10 mg. No irritation at injection site.
	Daily dosing intravenous	Beagle dog	3/3 Groups 2 + 3 5/5 Groups 1 + 4	0, 1, 5, 20	No toxic effect level 10 mg/kg/day. Clinical signs at all dose levels. No irritation at injection site. No toxic effect level 20 mg/kg/day.
Six Month Toxicity	Daily dosing oral	Wistar rat	30/30	0, 25, 100, 400	Flushed extremities at all dose levels. Low incidence of minimal thyroid hypertrophy at 400 mg/day. Slight increase in liver weight at 400 mg/day. Sporadic deaths at 400 mg/kg/day.
	Daily dosing oral	Beagle dog	3/3 Groups 2 + 3 5/5 Groups 1 + 4	0, 5, 25, 100	No toxic effect level 100 mg/kg/day. Clinical signs at all dose levels which reduced on continued dosing. One dog treated with 25 mg/kg was killed due to severe clinical signs.
Twelve Month Toxicity	Daily dosing oral	Beagle dog	4/4 Groups 2 + 3 6/6 Groups 1 + 4	0, 5, 25, 100	No toxic effect level 100 mg/kg/day. Clinical signs at all dose levels. One 5 mg male and one 25 mg sacrificed because of aggression. One 100 mg male died on day 280. No toxic effect level 25 mg/kg/day.

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PART III: CONSUMER INFORMATION**Pr Mylan-Zolmitriptan ODT**

zolmitriptan orally disintegrating tablets

2.5 mg

This leaflet is part III of a three-part "Product Monograph" published when Mylan-Zolmitriptan ODT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Mylan-Zolmitriptan ODT. Contact your doctor or pharmacist if you have any questions about the drug.

REMEMBER: this medicine was prescribed only for YOU. Only a doctor knows who can use it safely. Never give it to someone else. It may harm them, even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

The name of your medicine is Mylan-Zolmitriptan ODT which can only be obtained by prescription from your doctor. The decision to use Mylan-Zolmitriptan ODT is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are a post-menopausal female, or a male over 40), tell your doctor. Your doctor should evaluate you for heart disease in order to determine if Mylan-Zolmitriptan ODT is appropriate for you.

WHAT THE MEDICATION IS USED FOR:

Mylan-Zolmitriptan ODT belongs to a group of anti-migraine drugs called 5-HT₁ agonists. Mylan-Zolmitriptan ODT is used to relieve your migraine headache and other associated symptoms of a migraine attack.

Mylan-Zolmitriptan ODT should not be used continuously to prevent or reduce the number of attacks you experience. Use Mylan-Zolmitriptan ODT only to treat an actual migraine headache attack.

WHAT IT DOES:

Migraine headache is believed to be caused by a widening of the blood vessels in the head. Mylan-Zolmitriptan ODT narrows the vessels and relieves the pain and other symptoms of migraine headache.

WHEN IT SHOULD NOT BE USED:

Mylan-Zolmitriptan ODT should not be used if:

- you are allergic to zolmitriptan or any of the other ingredients in Mylan-Zolmitriptan ODT (see "WHAT THE NONMEDICINAL INGREDIENTS ARE")

- you have a history, or any symptoms or signs of a heart condition
- you have severe or uncontrolled hypertension
- you are taking or have recently taken (within 24 hours) an ergotamine containing or ergot-like drug, or another triptan used to treat migraines
- you have another type of headache that is different from a migraine attack
- you are taking or have recently taken (within 2 weeks) a monoamine oxidase inhibitor (MAOI)

WHAT THE MEDICINAL INGREDIENT IS:

Mylan-Zolmitriptan ODT contains 2.5 mg of zolmitriptan as the active ingredient.

WHAT THE NONMEDICINAL INGREDIENTS ARE:

Mylan-Zolmitriptan ODT contains: aspartame, colloidal silicon dioxide, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, and orange flavour (artificial). Each 2.5 mg Mylan-Zolmitriptan ODT contains 2.8 mg of phenylalanine.

WHAT DOSAGE FORMS IT COMES IN:

Mylan-Zolmitriptan ODT is supplied in orally disintegrating tablets of 2.5 mg in blister packs containing 6 tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use Mylan-Zolmitriptan ODT talk to your doctor or pharmacist if the answer to any of the following questions is YES, or if you do not know the answer:

- Are you pregnant, think you might be pregnant, or trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you or have you ever experienced any pain or tightness in the chest, (which may or may not spread to your neck, jaw, or upper arm), shortness of breath, or irregular heart beats? Do you have angina? Have you ever had heart or blood vessel disease? Do you have a history of cerebral bleeding? Have you had a heart attack or stroke?
- Do you have risk factors for heart disease, such as: high blood pressure, high cholesterol, smoking, obesity, diabetes, or strong family history of heart disease?
- Do you have a condition called phenylketonuria (a specific blood disorder)?
- Are you post-menopausal or a male over 40?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine 5-HT₁ agonist medications such as sumatriptan succinate, naratriptan hydrochloride, rizatriptan benzoate, almotriptan malate or migraine medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medications for depression such as selective serotonin reuptake inhibitors (SSRI's), for

example, fluoxetine hydrochloride, sertraline hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, etc., or serotonin norepinephrine reuptake inhibitors (SNRIs), for example, venlafaxine hydrochloride, or monoamine oxidase inhibitors (MAOIs), for example, phenelzine sulfate, tranylcypromine sulfate or moclobemide?

- Have you ever experienced numbness on one side of your body when you have a headache?
- Have you ever had epilepsy or seizures?
- Have you ever had liver disease?
- Are you over 65 years of age?
- Is this headache different from your usual migraine attacks?
- Are you taking cimetidine (for treatment of indigestion or stomach ulcers) or a member of the quinolone family of antibiotics (for example ciprofloxacin)?

If you use Mylan-Zolmitriptan ODT too often, it may make your headaches worse. If this happens, your doctor may tell you to stop taking Mylan-Zolmitriptan.

Use of Mylan-Zolmitriptan ODT during pregnancy: Do not use Mylan-Zolmitriptan ODT if you are pregnant, think you might be pregnant, are trying to become pregnant or are using inadequate contraception, unless you have discussed this with your doctor.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any other drugs you take, including:

- other 5-HT₁ agonist migraine drugs (sumatriptan succinate, naratriptan hydrochloride, rizatriptan benzoate, almotriptan malate) or migraine drugs that contain ergotamine, dihydroergotamine, methysergide
- drugs for depression such as selective serotonin reuptake inhibitors (SSRI's), for example, fluoxetine hydrochloride, sertraline hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, etc., or serotonin norepinephrine reuptake inhibitors (SNRIs), for example, venlafaxine hydrochloride, or monoamine oxidase inhibitors (MAOIs), for example, phenelzine sulfate, tranylcypromine sulfate or moclobemide
- drugs used to treat upset stomach or stomach ulcers (cimetidine)
- antibiotics from the quinolone family (for example ciprofloxacin)

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that can be bought without a prescription.

PROPER USE OF THIS MEDICATION

USUAL DOSE:

Adults

The usual dosage is 2.5 mg, or lower if recommended by your doctor. The Mylan-Zolmitriptan 2.5 mg orally disintegrating tablets cannot be broken in half. The dose should be taken as soon as your migraine appears, but it may be taken at any time during your migraine headache.

For Mylan-Zolmitriptan orally disintegrating tablets, the blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil). The Mylan-Zolmitriptan ODT tablet should be placed on the tongue, where it will dissolve with the saliva. Water is not needed for the disintegrating tablet.

A second dose may be taken if your headache returns, but not sooner than 2 hours following the first tablet. For any attack where you have no response to the first dose, do not take a second dose without first consulting your doctor.

Do not administer more than 10 mg in any 24 hour period.

OVERDOSE:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Although the vast majority of Mylan-Zolmitriptan ODT users have not experienced any significant problems, you should be aware that the following side effects may occur.

Commonly reported side effects of Mylan-Zolmitriptan ODT are:

- feeling sick
- vomiting
- dizziness
- tiredness
- weakness

Mylan-Zolmitriptan ODT may cause drowsiness. Do not drive or operate machinery until you are sure that you are not drowsy.

Other common side effects include:

- muscle aches and pains
- difficulty swallowing
- dry mouth
- headache
- stomach pain

Uncommon side effects include:

- increase in the production of urine or in the frequency of urination

Tell your doctor of these symptoms at your next visit.

Migraineurs may be at risk of certain cerebrovascular events such as cerebral bleeding and stroke. In very rare cases, as with other drugs of this type, such diseases have been reported in association with the use of zolmitriptan.

In very rare cases, as with other drugs of this type (5HT₁ agonists), the following side effects have been reported:

- spasm of the blood vessels of the heart
- spasm of the blood vessels of the Gastro-Intestinal tract and spleen with possible infarctions

See the following table for what to do about serious side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Common (frequency greater than or equal to 1% but in less than 10% of patients)			
Irregular heart beat		✓	
Sensations of pain, pressure or tightness in the chest, neck, throat, jaw, arms, or legs			✓
Sensations of tingling, heat, heaviness or pressure			✓
Uncommon (frequency greater than or equal to 0.1% but in less than 1% of patients)			
Fast heart rate		✓	
Temporary increase in blood pressure		✓	
Rare (frequency greater than or equal to 0.01% but in less than 0.1% of patients)			
Shortness of breath, wheeziness, heart throbbing, swelling of the eyelids, face, or lips; or a skin rash, itchy rash, skin lumps or hives, or swelling with fluid in the tissues			✓
Very rare (frequency in less than 0.01% of patients)			
Symptoms of a heart attack (chest pain, sweating, shortness of breath)			✓
Sudden or severe abdominal pain or bloody diarrhea			✓

For any unexpected effects while taking Mylan-Zolmitriptan ODT, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Mylan-Zolmitriptan ODT could be harmful to children. Store your medication between 15°C and 30°C, away from direct heat.

If your doctor decides to stop your treatment, return your medicine to the pharmacist for disposal. Do not take your medication after the expiry date on the package and blister foil. Return the tablets to your pharmacist for disposal.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at: 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to: 1-866-678-6789, or
 - Mail to: Canada Vigilance National Office
Health Canada
Postal Locator 0701E
Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guideline are available on the MedEffect™ Canada Web Site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

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