PRODUCT MONOGRAPH

[Pr] MINT-ZOLMITRIPTAN

Zolmitriptan Tablets

2.5 mg

[Pr] MINT-ZOLMITRIPTAN ODT

Zolmitriptan Orally Disintegrating Tablets

2.5 mg

$5\text{-}HT_1$ Receptor Agonist

MIGRAINE THERAPY

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Product	Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
MINT-ZOLMITRIPTAN	oral	conventional tablet / 2.5 mg	anhydrous lactose
MINT-ZOLMITRIPTAN ODT	oral	orally dispersible tablet / 2.5 mg	none

* For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

INDICATIONS AND CLINICAL USE

Adults

MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT (zolmitriptan) is indicated for the acute treatment of migraine attacks with or without aura.

MINT-ZOLMITRIPTAN / MINT-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 MINT-ZOLMITRIPTAN/MINT-ZOLMITRIPTAN ODT 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

MINT-ZOLMITRIPTAN / MINT-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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT. 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT can give rise to increases in blood pressure (see WARNINGS AND PRECAUTIONS, Hematologic);**

- **within 24 hours of treatment with another 5-HT_1 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

MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT (zolmitriptan) should only be

used where a clear diagnosis of migraine has been established.

Lactose: Lactose is a non-medicinal ingredient in MINT-ZOLMITRIPTAN tablets. Therefore, patients with rare hereditary problems of galactose intolerance (the Lapp lactase deficiency or glucose- galactose malabsorption) should not take MINT-ZOLMITRIPTAN tablets.

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 **MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT** 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-HT_1 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.

MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT not be given to patients in whom unrecognised 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, MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT, 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT, 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT.

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-HT_1 agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following **MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT** 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 **MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT** administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Cardiac Events and Fatalities Associated with 5-HT_1 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-HT_1 agonists. Considering the extent of use of 5-HT_1 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT.

Premarketing Experience with Zolmitriptan

Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of zolmitriptan conventional tablets, 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-HT_1 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-HT_1 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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-HT_1 Agonist

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 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-HT_1 agonist is not known. Similar studies have not been done with zolmitriptan. However, owing to the common pharmacodynamic actions of 5-HT_1 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-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Peripheral vascular ischemia has been reported with 5-HT_1 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-HT_1 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, MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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-HT_1 agonists. MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS).

Dependence

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

Hepatic

MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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-HT_1 agonists such as MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT. 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, MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 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-HT_1 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT.

Seizures: Caution should be observed if MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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. MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPAN / MINT-ZOLMITRIPTAN ODT 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:

MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 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 reported as follows:

Very common (≥10%)

Common (≥1% - <10%)

Uncommon (≥0.1% - <1%)

Rare (≥0.01% - <0.1%)

Very Rare (<0.01%)

Experience in Controlled Clinical Trials with zolmitriptan

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 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-HT_1 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 WITH ZOLMITRIPTAN CONVENTIONAL TABLET (zolmitriptan)

Acute Safety: In placebo-controlled migraine trials, 1,673 patients received at least one dose of zolmitriptan. The following table (Table 1) lists adverse events that occurred in five placebo- controlled clinical trials in migraine patients. Events that occurred at an incidence of 1% or more in any one of the zolmitriptan 1 mg, 2.5 mg or 5 mg dose groups and that occurred at a higher incidence than in the placebo group are included. The events cited reflect experience gained under closely monitored conditions in 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 behaviour, 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 Treatment Emergent Adverse Events in Five Single-Attack Placebo-Controlled Migraine Trials, Reported by ≥1% Patients Treated With zolmitriptan

	Placebo	Zolmitriptan 1 mg	Zolmitriptan 2.5 mg	Zolmitriptan 5 mg
Number of patients	401	163	498	1012
		% incidence		
Symptoms of potential cardiac origin:				
Neck/Throat/Jaw Sensations*	3.0	6.1	7.0	10.9
Chest/Thorax sensations*	1.2	1.8	3.4	3.8
Upper Limb Sensations*	0.5	2.4	4.2	4.1
Palpitations	0.7	0	0.2	2.2
Other Body Systems:				
Neurological:				
Dizziness	4.0	5.5	8.4	9.5
Nervousness	0.2	0	1.4	0.7
Somnolence	3.0	4.9	6.0	7.7

Table 1 **Treatment Emergent Adverse Events in Five Single-Attack Placebo-Controlled Migraine Trials, Reported by ≥1% Patients Treated With zolmitriptan**

	Placebo	Zolmitriptan 1 mg	Zolmitriptan 2.5 mg	Zolmitriptan 5 mg
Number of patients	401	163	498	1012
Thinking Abnormal	0.5	0	1.2	0.3
Temor	0.7	0.6	1.0	0.7
Vertigo	0	0	0	1.5
Hyperesthesia	0	0	0.6	1.1
Digestive:				
Diarrhea	0.5	0.6	1.0	0.6
Dry mouth	1.7	4.9	3.2	3.2
Dyspepsia	0.5	3.1	1.6	1.0
Dysphagia	0	0	0	1.8
Nausea	3.7	3.7	9.0	6.2
Vomit	2.5	0.6	1.4	1.5
Miscellaneous:				
Asthenia	3.2	4.9	3.2	8.8
Limb Sensations (upper and lower)*	0.7	0.6	0.4	1.6
Limb Sensations (lower)*	0.7	1.2	0.4	1.8
Sensations - location unspecified*	5.2	4.9	5.8	9.2
Abdominal Pain	1.7	1.2	0.6	1.3
Reaction Aggravated	1.0	1.2	1.0	0.7
Head/face Sensations*	1.7	6.7	8.6	10.9
Myalgia	0.2	0	0.2	1.3
Myasthenia	0.2	0	0.6	1.9
Dyspnea	0.2	0.6	0.2	1.2
Rhinitis	0.2	1.2	1.2	0.9
Sweating	1.2	0	1.6	2.5
Taste Perversion	0.5	2.5	0.6	0.7

* The term sensation encompasses adverse events described as pain, discomfort, pressure, heaviness, tightness, heat/burning sensations, tingling and paresthesia

Zolmitriptan is generally well tolerated. Across all doses, most adverse events were mild to moderate in severity as well as transient and self-limiting. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of 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.

Long Term Safety: In a long-term open label study in which patients were allowed to treat multiple migraine attacks for up to one year, 8% (167 of 2,058) of patients withdrew from the study due to an adverse experience. In this study, migraine headaches could be treated with either a single 5 mg dose of zolmitriptan, or an initial 5 mg dose followed by a second 5 mg dose if necessary (5+5 mg). The most common adverse events (defined as occurring at an incidence of at least 5%) recorded for the 5 mg and 5+5 mg doses, respectively, comprised, in descending order of frequency: neck/throat sensations* (16%, 15%),

head/face sensations* (15%, 14%), asthenia (14%, 14%), sensations* location unspecified (12%, 11%), limb sensations* (11%, 11%), nausea (12%, 8%), dizziness (11%, 9%), somnolence (10%, 10%), chest/thorax sensations* (7%, 7%), dry mouth (4%, 5%), and hyperesthesia (5%, 4%). Due to the lack of a placebo arm in this study, the role of zolmitriptan in causation cannot be reliably determined. (*See footnote for Table 1). The long term safety of a 2.5 mg dose was not assessed in this study.

Other Events: The frequencies of less commonly reported adverse clinical events are presented below. Because the reports include events observed in open and uncontrolled studies, the role of zolmitriptan 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 zolmitriptan (n=4,027) and reported an event divided by the total number of patients exposed to zolmitriptan. 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 body system categories and enumerated in order of decreasing frequency.

Atypical sensation: Uncommon was hyperesthesia.

General: Uncommon were allergy reaction, chills, facial edema, fever, malaise and photosensitivity.

Cardiovascular: Uncommon were arrhythmias, hypertension and syncope. Rare were bradycardia, extrasystoles, postural hypotension, QT prolongation, and thrombophlebitis. Rare reports of tachycardia, palpitations and transient increases in systemic blood pressure in patients with or without a history of hypertension (see WARNINGS AND PRECAUTIONS, Cardiovascular, Increased Blood Pressure).

Digestive: Uncommon were increased appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality and thirst. Rare were anorexia, constipation, gastritis, hematemesis, pancreatitis, melena and ulcer.

Hemic: Uncommon was ecchymosis. Rare were cyanosis, thrombocytopenia, eosinophilia and leucopenia.

Metabolic: Uncommon was edema. Rare were hyperglycemia and alkaline phosphatase increased.

Musculoskeletal: Uncommon were back pain, leg cramps and tenosynovitis. Rare were arthritis, tetany and twitching.

Neurological: Uncommon were agitation, anxiety, depression, emotional lability and insomnia. Rare were akathesia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertonia, irritability and headache.

Respiratory: Uncommon were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis and yawn. Rare were apnea and voice alteration.

Skin: Uncommon were pruritus, and rash. Rare reports were urticaria and angioedema.

Special Senses: Uncommon were dry eye, eye pain, hyperacusis, ear pain, parosmia, and tinnitus. Rare were diplopia and lacrimation.

Urogenital: Uncommon were hematuria, cystitis, polyuria, urinary frequency and urinary urgency. Rare were miscarriage and dysmenorrhea.

EXPERIENCE IN CONTROLLED CLINICAL TRIALS WITH ZOLMITRIPTAN ORALLY DISINTEGRATING TABLETS (zolmitriptan)

Acute Safety: In an international, placebo-controlled, double-blind trial to evaluate the efficacy and tolerability of zolmitriptan orally disintegrating tablets 2.5 mg in the acute treatment of adult patients with migraine, 231 patients received at least one dose of zolmitriptan orally disintegrating tablets. 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 orally disintegrating tablets 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. 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 and consistent with those observed in Tables 1 and 2.

Adverse Drug Reactions in Special Population

Adolescents (12-17 years of age)

Table 3 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 3 **Adverse events in a single placebo-controlled adolescent study, reported by ≥1% of patients treated with zolmitriptan**

Body System and Adverse Event (COSTART term)	Percentage of Patients			
		Zolmitriptan		
	Placebo (N=176)	**2.5 mg** (N=171)	**5 mg** (N=174)	**10 mg** (N=178)
Cardiovascular				
Vasodilation	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-HT_1 Agonists: The administration of zolmitriptan with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT_1 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

The following general statements apply to MINT-ZOLMITRIPTAN and MINT-ZOLMITRIPTAN ODT.

MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT (zolmitriptan) is recommended only for the acute treatment of migraine attacks. MINT-ZOLMITRIPTAN / MINT-

ZOLMITRIPTAN ODT should not be used prophylactically.

The recommended adult starting dose for MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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: MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT 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 MINT-ZOLMITRIPTAN / MINT-ZOLMITRIPTAN ODT in any 24 hour period (see DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

MINT-ZOLMITRIPTAN CONVENTIONAL TABLETS

Adults: The minimal effective single adult dose of MINT-ZOLMITRIPTAN is 1 mg. The recommended single dose is 2.5 mg. The 1 mg dose can be approximated by manually breaking a 2.5 mg conventional tablet in half.

In controlled clinical trials, single doses of 1 mg, 2.5 mg or 5 mg zolmitriptan conventional tablets were shown to be effective in the acute treatment of migraine headaches. In the only direct comparison of the 2.5 and 5 mg doses, there was little added benefit from the higher dose, while side effects increased with 5 mg zolmitriptan tablets (see ADVERSE EVENTS, Table 1, and Part II: CLINICAL TRIALS, Table 4).

MINT-ZOLMITRIPAN ODT

Adults: The minimal effective single adult dose of MINT-ZOLMITRIPAN ODT is 1 mg. The recommended single dose is 2.5 mg. **The MINT-ZOLMITRIPTAN ODT 2.5 mg orally dispersible tablet cannot be broken in half to approximate a 1 mg dose.**

The MINT-ZOLMITRIPTAN ODT orally dispersible tablet rapidly dissolves when placed on the

tongue and is swallowed with the patient's saliva. MINT-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

MINT-ZOLMITRIPTAN CONVENTIONAL TABLETS

The tablet should be swallowed with water.

MINT-ZOLMITRIPTAN ODT

The tablet should be placed on the tongue, where it will dissolve with the saliva. Water is not needed for the dispersible 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-hydroxytryptamine$_1$ (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-HT$_2$, 5-HT$_3$, 5-HT$_4$, alpha$_1$, alpha$_2$, or beta$_1$, -adrenergic; H$_1$, H$_2$, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$, 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 anastamoses, and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

Pharmacokinetics

ZOLMITRIPTAN CONVENTIONAL TABLETS AND ZOLMITRIPTAN ORALLY DISINTEGRATING TABLETS

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.

The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. Because of the similarity in exposure zolmitriptan tablets and nasal spray should have similar dosage adjustments and 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 ($t_{½}$) 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 $t_{½}$ 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. Zomitriptan 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 (ClCr ≥5 - ≤25 mL/min), clearance of zolmitriptan was reduced by 25% compared to normal (ClCr ≥70 mL/min). There was no significant change observed in the clearance of zolmitriptan in patients with moderate renal impairment (ClCr ≥26 - ≤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

MINT-ZOLMITRIPTAN conventional tablets and MINT-ZOLMITRIPTAN ODT should be stored at room temperature between 15 and 30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

MINT-ZOLMITRIPTAN 2.5 mg conventional tablets are light pink coloured, round, film coated tablets, debossed with "**2.5**" on one side and plain on the other side. Available in blister packs of 3 tablets with two packs packaged in each carton (6 tablets total per box).

MINT-ZOLMITRIPTAN ODT 2.5 mg tablets are white, round shaped, flat face, beveled edge tablets, debossed with '**C**' on one side and '**J**' on other side, having a characteristic flavour. Available in blister packs of 3 tablets with two packs packaged in each carton (6 tablets total per box).

Composition

MINT-ZOLMITRIPTAN conventional tablets

Nonmedicinal ingredients: HPMC 2910/hypromellose 5 cP, iron oxide red, lactose anhydrous, macrogol/peg 400, macrogol/peg 8000, magnesium stearate, microcrystalline cellulose, purified water, sodium starch glycolate titanium dioxide.

MINT-ZOLMITRIPTAN ODT

Nonmedicinal ingredients: acesulfame potassium , acetone, amino methacrylate copolymer, colloidal silicon dioxide, crospovidone, isopropyl alcohol, low-substituted hydroxypropyl cellulose, magnesium aluminometasilicate, magnesium stearate, maltodextrin, mannitol, modified corn starch, natural flavours, purified water, sodium lauryl sulphate, talc.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

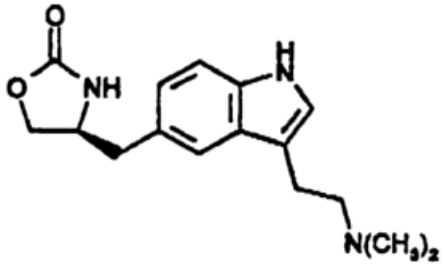
Drug Substance

Common Name: Zolmitriptan

Chemical Name: (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone

Molecular Formula and Molecular Mass: $C_{16}H_{21}N_3O_2$ and 287.36

Structural Formula:



Physiochemical Properties: White to almost white powder

Solubility: slightly soluble in water (1.3 mg/mL at 25 ºC), 0.1M hydrochloric acid (33 mg/mL at 25 ºC)

pKa: 9.64 ± 0.01

Partition co-efficient: octanol-1-ol/water partition log KD=-1.0

Melting point: 136 ºC

CLINICAL TRIALS

A randomized, blinded, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study comparing the Test product Mint-Zolmitriptan (zolmitriptan 2.5 mg film-coated tablets of Mint Pharmaceuticals Inc.) with the Reference product Zomig® (zolmitriptan
2.5 mg tablets of AstraZeneca Canada Inc.) was conducted in healthy adult, human subjects under fasting conditions (N = 37). The results are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Zolmitriptan (1 x 2.5 mg) Tablet From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUCT (pg*hr/mL)	28201.40 30833.63 (44.50)	26550.62 29791.64 (51.16)	106.22	97.97 - 115.16
AUCI (pg*hr/mL)	29230.00 31863.89 (43.93)	27568.13 30828.10 (50.23)	106.03	98.21 - 114.47
C_{max} (pg/mL)	5758.80 6142.41 (32.33)	5361.39 5785.25 (39.38)	107.41	97.20 - 118.70
T_{max} (hr)¥	1.35 (69.06)	1.311 (66.43)		
T½ (h)¥	4.95 (47.86)	4.59 (55.36)		

* MINT-ZOLMITRIPTAN (zolmitriptan) 2.5 mg film-coated tablets, Mint Pharmaceuticals Inc. in Canada
† Zomig® (zolmitriptan) 2.5 mg tablets by AstraZeneca Canada Inc. purchased in Canada.
¥ Expressed as the arithmetic mean (CV%) only.

A randomized, blinded, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study comparing the Test Product Mint-Zolmitriptan ODT (zolmitriptan 2.5 mg orally disintegrating tablets of Mint Pharmaceuticals Inc.) with the Reference Product ZOMIG RAPIMELT® (zolmitriptan 2.5 mg orally disintegrating tablets of AstraZeneca Canada Inc.) was conducted in 30 healthy adult, human subjects, under fasting conditions. Please find the results below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Zolmitriptan (1 x [2.5 mg]) Orally Disintegrating Tablet From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
AUCT (pg*hr/mL)	25109.60 27618.42 (38.58)	25683.96 27396.82 (36.11)	97.76	85.52 - 111.76
AUCI (pg*hr/mL)	25805.85 28304.75 (38.05)	26431.29 28095.99 (35.39)	97.63	85.75 - 111.16
Cmax (pg/mL)	4975.65 5308.78 (36.72)	4733.96 4987.38 (32.01)	105.11	92.45 - 119.49
Tmax (hr) ¥	2.71 (50.26)	2.38 (54.57)		
T½ (h) ¥	4.08 (35.84)	3.83 (38.10)		

* MINT-ZOLMITRIPTAN ODT (zolmitriptan) 2.5 mg orally disintegrating tablets, Mint Pharmaceuticals Inc. in Canada.
† Zomig Rapimelt® (zolmitriptan) tablets 2.5 mg orally disintegrating tablets by AstraZeneca Canada Inc. purchased in Canada.
¥ 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-CONVENTIONAL TABLET

The efficacy of zolmitriptan conventional tablets in the acute treatment of migraine attacks was evaluated in five randomized, double blind, placebo controlled studies, of which 2 utilized the 1 mg dose, 2 utilized the 2.5 mg dose and 4 utilized the 5 mg dose. In all studies, the effect of zolmitriptan was compared to placebo in the treatment of a single migraine attack. All studies used the marketed formulation. Study 1 was a single-centre study in which patients treated their headaches in a clinic setting. In the other studies, patients treated their headaches as outpatients. In Study 4, patients who had previously used sumatriptan were excluded, whereas in the other studies no such exclusion was applied. Patients enrolled in

these five studies were predominantly female (82%) and Caucasian (97%) with a mean age of 40 years (range 12-65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed at 1, 2, and, in most studies, 4 hours after dosing. Associated symptoms such as nausea, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post dose. A second dose of zolmitriptan tablets or other medication was allowed 2 to 24 hours after the initial dose, to treat persistent and recurrent headache. The frequency and time to use of these additional treatments were also recorded.

Table 4 shows efficacy results for zolmitriptan conventional tablets in 5 placebo-controlled trials, 4 of which were multi-centre. The percentage of patients with pain relief (grade1/0) at 2 hours after treatment (the primary endpoint measure) was significantly greater among patients receiving zolmitriptan at all doses compared to those on placebo. In Study 3, which directly compared the 1 mg, 2.5 mg and 5 mg doses, there was a statistically significant greater proportion of patients with headache response at 2 hours in the higher dose groups (2.5 mg or 5 mg) than in the 1 mg group. There was no statistically significant difference between the 2.5 mg and 5 mg dose groups for the primary endpoint measure of pain relief (1/0) at 2 hours, or at any other time point measured.

Table 4 Percentage of Patients with Pain Relief (1/0)♦ at 2 Hours - Intent to Treat Population

Study	Hour Post-dose	Placebo	Zolmitriptan Conventional Tablet Dose (mg)		
			1	2.5	5
		%	%	%	%
1	2	15 (N=20)	27 (N=22)	-	62† (N=21)
2	2	21 (N=99)	-	-	61 (N=213)
3	2	32 (N=140)	50† (N=141)	63†** (N=298)	65†** (N=280)
4	2	44 (N=56)	-	-	59B (N=498)
5	2	36 (N=101)	-	62† (N=200)	-

* p≤ 0.05 in comparison with placebo
** p≤ 0.01 in comparison with 1 mg
† p ≤ 0.01 in comparison with placebo
\- = Not studied
♦ Pain Relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain)

The proportion of patients being pain free at 2 hours was statistically significantly greater for patients receiving zolmitriptan conventional tablets at doses of 1, 2.5 and 5 mg compared with placebo in Study 3.

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

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The probability of taking a second zolmitriptan dose or other medication for migraine over 24 hours following the initial dose of study treatment was lower for zolmitriptan treated groups as compared to placebo. For the 1 mg dose, the probability of taking a second dose was similar to placebo and greater than with either the 2.5 or 5 mg dose.

In an open label study conducted to evaluate long-term safety, patients treated multiple migraine headaches with 5 mg doses of zolmitriptan for up to 1 year. A total of 31,579 migraine attacks were treated during the course of the study (mean number of headaches treated per patient was 15). An analysis of patients who treated at least 30 migraine attacks of moderate or severe intensity (n = 233) suggests that the 2 hour headache response rate is maintained with repeated use of zolmitriptan.

ZOLMITRIPTAN ORALLY DISINTEGRATING TABLETS

The efficacy and tolerability of zolmitriptan orally disintegrating tablets 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 orally disintegrating tablets group experienced a headache response within 2 hours of initial dosing (primary endpoint, see Table 5). Patients treating with zolmitriptan orally disintegrating tablets also had statistically significant headache response relative to placebo at 0.5, 1 and 4 hours post-dose.

Table 5 Percentage of Patients with Headache Response* at 2 Hours Post-Dose by Treatment Group (ITT Population)

Zolmitriptan orally disintegrating tablets Group		Placebo Treatment Group		Statistical Comparison of zolmitriptan orally disintegrating tablets 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 orally disintegrating tablets 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 orally disintegrating tablets (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 orally disintegrating tablets treatment group relative to placebo, 5 hours and 45 minutes versus 2 hours and 10 minutes.

The efficacy and tolerability of zolmitriptan orally disintegrating tablets 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 orally disintegrating tablets group experienced a pain-free response within 2 hours of dosing (see Table 6).

Table 6 Pain Free Response* at 2 Hours Post-Dose by Treatment Group (ITT Population)

Migraine Attack	zolmitriptan orally disintegrating tablets Group		Placebo Treatment Group		Statistical Comparison of zolmitriptan orally disintegrating tablets 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
1st attack[c]	278	114 (41)	282	55 (20)	Not analyzed[c]
2nd 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 orally disintegrating tablets treatment group and time to remedication was statistically significantly shorter in the placebo group ($p<0.001$).

Patients treating migraines with zolmitriptan orally disintegrating tablets 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-HT_1 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-HT_2, 5-HT_3, 5-HT_4, alpha$_1$, alpha$_2$, or beta$_1$, -adrenergic; H_1, H_2, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$, 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 (ED_{50} 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 $t_{½}$ of 1 to 2 hours. There were no apparent differences due to gender or route of administration. The $t_{½}$ 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 8.

In toxicity studies in which zolmitriptan nasal spray formulation was administered to rats (6 times daily for up to 6 months) and monkeys (8 times daily for 1 month) by the nasal route, the formulation was generally well tolerated. In monkeys, there was no indication of systemic toxicity or local irritation in the nasal cavity. In rats, a reversible minimal or mild rhinitis and nasopharyngitis was observed after 1 month at 72 mg/kg/day, with a no effect level of 18 mg/kg/day. This corresponds to approximately four-fold the maximum daily human exposure when expressed in terms of exposure per unit area of the nasal epithelium. There was no similar finding after 6 months of intranasal dosing at 72 mg/kg/day. Zolmitriptan nasal spray formulation is practically a non-irritant to the rabbit eye.

Table 8 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. No toxic effect level 100 mg/kg/day.
	Daily dosing oral	Beagle dog	3/3 Groups 2+3 5/5 Groups 1+4	0, 5, 25, 100	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. No toxic effect level 25 mg/kg/day.
One Month Toxicity	Daily dosing intravenous	Wistar rat	15/15	0, 0.5, 2, 10	Expected clinical signs at 2 and 10 mg. No irritation at injection site. No toxic effect level 10 mg/kg/day.
	Daily dosing intravenous	Beagle dog	3/3 Groups 2 + 3 5/5 Groups 1 + 4	0, 1, 5, 20	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. No toxic effect level 100 mg/kg/day.
	Daily dosing oral	Beagle dog	3/3 Groups 2 + 3 5/5 Groups 1 + 4	0, 5, 25, 100	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. No toxic effect level 100 mg/kg/day.
Twelve Month Toxicity	Daily dosing oral	Beagle dog	4/4 Groups 2 +3 6/6 Groups 1 + 4	0, 5, 25, 100	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.

TYPE	STUDY	SPECIES	No/GROUP M/F	DOSE mg/kg/day	FINDINGS
Nasal Administration					
One month Toxicity	Daily dosing Intranasally	Rat	40/40	0, 18, 36, 72	Clinical signs at all dose levels. Minor Rhinitis in high dose males and females, and mid-dose males. Nasopharyngitis in high dose males and females. No signs of systemic toxicity, NOEL 18 mg/kg/day.
One month Toxicity	Daily dosing Intranasally	Rat	Group 1: 20/20 Group 2, 3: 10/10	0, 72	Treatment well tolerated. Rhinitis and Nasopharyngitis of minimal to mild severity was observed, with histopathological effects being reversible.
Six month Toxicity	Daily dosing Intranasally	Rat	Groups 1, 5: 30/30 Groups 2, 3, 4: 20/20	0, 6, 18, 72	Treatment was well tolerated and there were no histopathological findings attributable to either the dosing regime or the nasal spray.
One month Toxicity	3 Times Daily Dosing Intranasally	Monkey	Group 1, 4: 6/6 Group 2, 3: 3/3	0, 15, 30	No associated changes suggestive of local irritancy or overt systemic toxicity
One month Toxicity	Up to 8 times a day, Intranasally	Monkey	Groups 1, 2, 3: 3/3	0, 16, 32, 64	Systemic exposure was demonstrated at all dose levels and no signs of systemic toxicity or local irritation were observed

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17. Product Monograph ZOMIG® (zolmitriptan) 2.5 mg tablets and ZOMIG RAPIMELT® (zolmitriptan) 2.5 mg orally disintegrating tablets by AstraZeneca Canada Inc. (Control # 158295); Date of Revision: November 1, 2012.

PART III: CONSUMER INFORMATION
PrMINT-ZOLMITRIPTAN and PrMINT-ZOLMITRIPTAN ODT
(zolmitriptan)

This leaflet is part III of a three-part "Product Monograph" published when MINT-ZOLMITRIPTAN and MINT-ZOLMITRIPTAN ODT were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MINT-ZOLMITRIPTAN and MINT-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 MINT-ZOLMITRIPTAN or MINT-ZOLMITRIPTAN ODT which can only be obtained by prescription from your doctor. The decision to use MINT-ZOLMITRIPTAN / MINT-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 MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT are appropriate for you.

WHAT THE MEDICATION IS USED FOR:
MINT-ZOLMITRIPTAN and MINT-ZOLMITRIPTAN ODT belong to a group of anti- migraine drugs called 5-HT_1 agonists. MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT is used to relieve your migraine headache and other associated symptoms of a migraine attack.

MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT should not be used continuously to prevent or reduce the number of attacks you experience. Use MINT-ZOLMITRIPTAN /MINT-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. MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT narrows the vessels and relieves the pain and other symptoms of migraine headache.

WHEN IT SHOULD NOT BE USED:
MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT should not be used if:

- you are allergic to zolmitriptan or any of the other ingredients in MINT-ZOLMITRIPTAN /MINT-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:
Both MINT-ZOLMITRIPTAN and MINT-ZOLMITRIPTAN ODT tablets contain 2.5 mg of zolmitriptan as the active ingredient.

WHAT THE IMPORTANT NONMEDICINAL INGREDIENTS ARE:
MINT-ZOLMITRIPTAN contains: HPMC 2910/Hypromellose 5 cP , Iron Oxide Red, Lactose Anhydrous, Macrogol/Peg 400, Macrogol/Peg 8000, Magnesium Stearate, Microcrystalline Cellulose, Purified water, Sodium Starch Glycolate, Titanium Dioxide.

MINT-ZOLMITRIPTAN ODT contains: Acesulfame Potassium, Acetone, Amino Methacrylate Copolymer, Colloidal Silicon Dioxide, Crospovidone (Polyplasdone XL – 10), Isopropyl Alcohol, Low-Substituted Hydroxypropyl Cellulose, Magnesium Aluminometasilicate, Magnesium Stearate, Maltodextrin, Mannitol, Modified Corn Starch, Natural Flavours, Purified Water, Sodium Lauryl Sulphate, Talc.

WHAT DOSAGE FORMS IT COMES IN:
MINT-ZOLMITRIPTAN is supplied in conventional tablets of 2.5 mg in blister packs containing 6 tablets. MINT-ZOLMITRIPTAN ODT is supplied in orally dispersible tablets of 2.5 mg in blister packs containing 6 tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use MINT-ZOLMITRIPTAN /MINT-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 rare hereditary problems of galactose intolerance?
- 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-HT_1 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 MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT too often, it may make your headaches worse. If this happens, your doctor may tell you to stop taking MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT.

MINT-ZOLMITRIPTAN tablets contain lactose which is a type of sugar. If you have been told by your doctor that you cannot tolerate or digest milk or some sugars, talk to your doctor before taking this medicine.

Use of MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT during pregnancy: Do not use MINT-ZOLMITRIPTAN or MINT-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-HT_1 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. A lower dose can be obtained by manually breaking a conventional tablet in half. The MINT-ZOLMITRIPTAN ODT 2.5 mg orally dispersible 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. Swallow your dose with water.

For MINT-ZOLMITRIPTAN ODT orally dispersible tablets, the blister pack should be peeled open as shown on the foil (tablets should not be pushed through the foil). The MINT-ZOLMITRIPTAN ODT tablet should be placed on the tongue, where it will dissolve with the saliva. Water is not needed for the dispersible 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:
If you have taken more medication than your doctor has instructed, contact either your doctor, hospital emergency department, or nearest poison control centre immediately.

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 zolmitriptan conventional tablets and zolmitriptan orally disintegrating tablets users have not experienced any significant problems, you should be aware that the following side effects may occur.

Commonly reported side effects of zolmitriptan conventional tablets and zolmitriptan orally disintegrating tablets are:

- feeling sick
- vomiting
- dizziness
- tiredness
- weakness

MINT-ZOLMITRIPTAN / MINT-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 ($5HT_1$ 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 call your doctor or pharmacist
	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 MINT-ZOLMITRIPTAN /MINT-ZOLMITRIPTAN ODT, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. MINT-ZOLMITRIPTAN and MINT-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 Program
    Health Canada
    Ottawa, ON K1A 0K9
    Postal Locator 0701E

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

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

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: or by contacting the sponsor, Mint Pharmaceuticals Inc. at: Mint Pharmaceuticals Inc.,
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This leaflet was prepared by Mint Pharmaceuticals Inc.

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