PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNRA-ZOLMITRIPTAN

zolmitriptan tablets

tablets, 2.5 mg, oral

USP

5-HT_1 Receptor Agonist

Migraine Therapy

Nora Pharma Inc.
1565 boul. Lionel-Boulet
Varennes, QC, Canada
J3X 1P7

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	03/2025
7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	03/2025

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NRA-ZOLMITRIPTAN (zolmitriptan tablets) is indicated for:

- the acute treatment of migraine attacks with or without aura, in adults.

NRA-ZOLMITRIPTAN is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see 2 CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache, which is present in an older, predominantly male population.

1.1 Pediatrics

Pediatrics (<6 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in this pediatric population (see 7.1.3 Pediatrics).

Pediatrics (6 -17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of zolmitriptan in pediatric patients 6-17 years of age has not been established; therefore, Health Canada has not authorized an indication for use in this pediatric population (see 7.1.3 Pediatrics).

1.2 Geriatrics

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 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

NRA-ZOLMITRIPTAN (zolmitriptan) is contraindicated:

- 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 NRA-ZOLMITRIPTAN. Ischemic cardiac syndromes include, but are not restricted to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).
- in patients with uncontrolled or severe hypertension, as NRA-ZOLMITRIPTAN can give

rise to increases in blood pressure (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

- within 24 hours of treatment with another 5-HT1 agonist, or an ergotamine-containing or ergot- type medication like dihydroergotamine or methysergide (see 9.4 Drug-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 9.4 Drug-Drug Interactions).
- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Risk of Myocardial Ischemia and/or Myocardial Infarction:** Serious adverse cardiac events, including acute myocardial infarction, have been reported to occur within a few hours of zolmitriptan administration. NRA-ZOLMITRIPTAN is contraindicated for use in patients who have documented ischemic or vasospastic coronary artery disease (see 2 CONTRAINDICATIONS). NRA-ZOLMITRIPTAN should not be given to patients who have risk factors for coronary artery disease (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).
- **Cardiac Arrythmias:** Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death have been reported within a few hours of zolmitriptan administration (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).
- **Angina Pectoris:** NRA-ZOLMITRIPTAN may cause coronary artery vasospasm (Prinzmetal angina), even in patients without a history of coronary artery disease (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).
- **Cerebrovascular Events:** Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT1 agonists, and some have resulted in fatalities (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The following general statements apply to all dosage formulations of zolmitriptan.

- NRA-ZOLMITRIPTAN should only be used where a clear diagnosis of migraine has been established.

- NRA-ZOLMITRIPTAN is not indicated for prophylaxis of migraine.
- Lactose is a non-medicinal ingredient in NRA-ZOLMITRIPTAN tablets. Patients with hereditary problems of galactose intolerance should not take NRA-ZOLMITRIPTAN tablets(see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING; 7 WARNINGS AND PRECAUTIONS - Endocrine and Metabolism).
- The recommended adult starting dose for NRA-ZOLMITRIPTAN is 2.5 mg. The maximum recommended single dose is 5 mg.
- 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, should the initial dose be ineffective.
- The safety of treating more than 3 migraine headaches with zolmitriptan in a one-month period has not been established.
- Patients with mild to moderate hypertension should be treated cautiously at the lowest effective dose. NRA-ZOLMITRIPTAN is contraindicated in patients with severe or uncontrolled hypertension (see 2 CONTRAINDICATIONS).
- Hepatic impairment reduces zolmitriptan clearance. Lower doses are recommended (see 4.2 Recommended Dose and Dosage Adjustment; 10.3 Pharmacokinetics).
- Patients taking cimetidine and other 1A2 inhibitors should not exceed a dose of 5 mg NRA-ZOLMITRIPTAN in any 24 hour period (see 9.4 Drug-Drug Interactions).

4.2 Recommended Dose and Dosage Adjustment

Adults (≥ 18 years of age):

NRA-ZOLMITRIPTAN (zolmitriptan tablets): The minimal effective single adult dose of NRA-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 tablet in half.

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 8.2 Clinical Trial Adverse Reactions; 14.1 Clinical Trials By Indication).

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics: The safety and efficacy of zolmitriptan in patients 65 years of age and older has not been established and its use in this population is not recommended (see 7.1.4 Geriatrics).

Hepatic Insufficiency: Zolmitriptan is metabolized primarily in the liver. Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and

significant elevation in blood pressure was observed in some patients. NRA-ZOLMITRIPTAN should be administered with caution to patients with moderate or severe hepatic impairment, using a dose lower than 2.5 mg. Total dose should not exceed 5 mg in 24 hours. Blood pressure monitoring is recommended (see 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic; 10.3 Pharmacokinetics).

Renal Insufficiency: No dosage adjustment is required in patients with a creatinine clearance ≥15 ml/min. NRA-ZOLMITRIPTAN should not be used in patients with end-stage renal disease (CrCl <15 mL/min).

4.3 Administration

NRA-ZOLMITRIPTAN (zolmitriptan tablets): The tablet should be swallowed with water. The 1 mg dose can be approximated by manually breaking a 2.5 mg tablet in half.

5 OVERDOSAGE

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 10.3 Pharmacokinetics), and therefore monitoring of patients after overdose with NRA-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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Formulation	Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
NRA-ZOLMITRIPTAN	oral	tablet, 2.5 mg zolmitriptan	anhydrous lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and the Film Coating ingredients containing the following: Hypromellose, Polyethylene glycol, Titanium dioxide and Yellow iron oxide.

Description

NRA-ZOLMITRIPTAN tablet, 2.5 mg is Pale yellow colored, round shaped, film coated tablets, debossed 'Z 2.5' on one side and plain on the other side. Available in blister pack of 6's.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

NRA-ZOLMITRIPTAN (zolmitriptan) should only be used where a clear diagnosis of migraine has been established.

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.

  NRA-ZOLMITRIPTAN should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see 2 CONTRAINDICATIONS). It is strongly recommended that NRA-ZOLMITRIPTAN 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, NRA-ZOLMITRIPTAN should not be administered (see 2 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 NRA-ZOLMITRIPTAN should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following NRA-ZOLMITRIPTAN administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

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

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

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

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

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of zolmitriptan. Because $5\text{-}HT_1$ agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following NRA-ZOLMITRIPTAN should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and

should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following NRA-ZOLMITRIPTAN administration should be evaluated for atherosclerosis or predisposition to vasospasm (see 2 CONTRAINDICATIONS

- **Cardiac Events and Fatalities Associated with 5-HT1 Agonists**

As with other triptans, zolmitriptan may cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-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 NRA-ZOLMITRIPTAN.

- **Pre-marketing Experience with Zolmitriptan**

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

- **Post-marketing Experience with Zolmitriptan**

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

- **Cerebrovascular Events and Fatalities With 5-HT1 Agonists**

Migraineurs may be at risk of certain cerebrovascular events. Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-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 NRA-ZOLMITRIPTAN in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, haemorrhage, TIA).

- **Special Cardiovascular Pharmacology Studies With Another 5-HT1 Agonist**

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-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 8.1 Adverse Reaction Overview). 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 2 CONTRAINDICATIONS). In patients with controlled hypertension, zolmitriptan should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

    In pharmacodynamic studies, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen in volunteers with 5 mg zolmitriptan. In the headache trials, vital signs were measured only in a small, single-centre inpatient study, and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 patients experienced 20 to 80 mm Hg elevations in systolic or diastolic blood pressure after a 10 mg zolmitriptan dose. Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension who received 5-HT_1 agonists. NRA-ZOLMITRIPTAN is contraindicated in patients with uncontrolled or severe hypertension (see 2 CONTRAINDICATIONS).

Dependence, Tolerance and/or Abuse Liability

Zolmitriptan has not been studied for its potential to cause dependence, tolerance and/or abuse. However, there may be a theoretical risk of the occurrence of one or more of these risks. Health Professionals should consider the patient's history of drug use and monitor appropriately.

Overuse of analgesics or other medications, such as triptans, can result in the worsening of headache symptoms (medication overuse headache) (see 7 WARNINGS AND PRECAUTIONS - Neurologic).

Driving and Operating Machinery

Although zolmitriptan did not interfere with psychomotor performance in healthy volunteers, some patients in clinical trials experienced sedation with zolmitriptan. While taking NRA-ZOLMITRIPTAN, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination until they are reasonably certain that NRA-ZOLMITRIPTAN does not affect them adversely.

Endocrine and Metabolism

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

Hepatic/Biliary/Pancreatic

NRA-ZOLMITRIPTAN should be administered with caution to patients with moderate or severe hepatic impairment, using a dose lower than 2.5 mg (see 4.1 Dosing Considerations; 4.2 Recommended Dose and Dosage Adjustment, 10.3 Pharmacokinetics .

Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as zolmitriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, NRA-ZOLMITRIPTAN should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists (see 8.2 Clinical Trial 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 NRA-ZOLMITRIPTAN.

- **Medication Overuse Headache (MOH):** Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications. In patients with MOH, discontinuation of NRA-ZOLMITRIPTAN may result in withdrawal symptoms, such as a transient worsening of headache (see 7 WARNINGS AND PRECAUTIONS - Dependence, Tolerance and/or Abuse Liability).
- **Seizures:** Caution should be observed if NRA-ZOLMITRIPTAN is to be used in patients with a history of epilepsy or structural brain lesions, which lower the convulsion threshold.
- **Serotonin toxicity / Serotonin syndrome:** Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with triptans, including zolmitriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs). Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:
    - Spontaneous clonus
    - Inducible clonus or ocular clonus with agitation or diaphoresis
    - Tremor and hyperreflexia
    - Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

If concomitant treatment with NRA-ZOLMITRIPTAN and SSRIs (e.g., fluoxetine, paroxetine, sertraline) or SNRIs (e.g., venlafaxine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Ophthalmologic

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. Animal studies suggest zolmitriptan may accumulate in melanin-rich tissues over time, which could cause toxicity in these tissues, with extended use (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of zolmitriptan for use during human pregnancy has not been established. NRA-ZOLMITRIPTAN should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals showed no apparent signs of teratogenicity (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

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 NRA-ZOLMITRIPTAN to nursing women. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

7.1.3 Pediatrics

- **Pediatrics (<6 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. (see 1.1 Pediatrics).

- **Pediatrics (6-17 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of zolmitriptan have not been established in patients 6-17 years of age. Therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics; 8.2.1 Clinical Trial Adverse Reactions – Pediatrics; 10.3 Pharmacokinetics).

Systemic exposure to the parent compound does not differ significantly between adolescents (aged 12- 17 years) and adults, however exposure to the active metabolite, 2-6 times more potent, is greater in adolescents (see 10.3 Pharmacokinetics).

Some clinically serious adverse events, reported as rare occurrences in adults, have been reported in pediatric patients (see 8.5 Post-Market Adverse Reactions).

7.1.4 Geriatrics

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 coronary artery disease, and experience blood pressure increases that may be more pronounced. Clinical studies did not include patients over 65 years of age. Its use in this age group is, therefore, not recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Zolmitriptan is generally well tolerated. Across all doses, most adverse reactions 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.

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT1 agonists. These events are very rare and most have been reported in patients with risk factors predictive of coronary artery disease. Events reported have included coronary artery vasospasm, transient myocardial ischemia, angina pectoris, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. (see 2 CONTRAINDICATIONS; 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

As with other 5HT1 agonists, 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 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

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.

There have been rare reports of hypersensitivity reactions including urticaria and angioedema (see 7 WARNINGS AND PRECAUTIONS - Immune).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Experience in Controlled Clinical Trials with Zolmitriptan Tablets

Acute Safety: In placebo-controlled migraine trials, 1,673 patients received at least one dose of zolmitriptan. The following table (Table 2) 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 2 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
Thinking Abnormal	0.5	0	1.2	0.3
Tremor	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

	Placebo	Zolmitriptan 1 mg	Zolmitriptan 2.5 mg	Zolmitriptan 5 mg
Number of patients	401	163	498	1012
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 2). The long term safety of a 2.5 mg dose was not assessed in this study.

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, vomiting and abdominal pain.

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 Table 2.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (6-11 years of age)

Health Canada has not authorized an indication for use in any pediatric population (see 1.1 Pediatrics).

Limited data from a single multicenter, double-blind, randomized, placebo-controlled, cross-over clinical trial involving 168 pediatric patients (6-11 years) with migraine headache suggest the type and severity of adverse reactions may be similar to those in adults. No new safety issues have been identified from the completed pediatric trial for the age group investigated. However, the safety database for this pediatric population is too limited for the accurate identification of common, less common, rare, or very rare adverse reactions or their frequencies.

While no definitive conclusions can be made regarding relative frequencies, some cardiac arrhythmias, reported as rare in adults, were reported more frequently in the pediatric population.

Pediatrics (12-17 years of age)

Health Canada has not authorized an indication for use in any pediatric population (see 1.1

Pediatrics; 8.5 Post-Market Adverse Reactions).

Table 3 lists the adverse events observed in a single randomized placebo-controlled study of 696 adolescent migraineurs aged 12-17 years (see 7.1.3 Pediatrics; 10.3 Pharmacokinetics).

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

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

Body System and Adverse Event (COSTART term)	Placebo (N=176)	Percentage of Patients Zolmitriptan Tablet 2.5 mg (N=171)	5 mg (N=174)	10 mg (N=178)
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

8.3 Less Common Clinical Trial Adverse Reactions

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.

Blood and lymphatic system disorders: ecchymosis, cyanosis, thrombocytopenia, eosinophilia and leucopenia.

Cardiac disorders: arrhythmias, hypertension, syncope, bradycardia, extrasystoles, postural hypotension, QT prolongation, thrombophlebitis, tachycardia, palpitations and transient increases in systemic blood pressure in patients with or without a history of hypertension (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

Ear and labyrinth disorders: hyperacusis, ear pain , tinnitus

Eye disorders: dry eye, eye pain, diplopia, lacrimation

Gastrointestinal disorders: increased appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality, thirst, anorexia, constipation, gastritis, hematemesis, pancreatitis, melena, ulcer

General disorders and administration site conditions: allergy reaction, chills, facial edema, fever, malaise, parosmia, photosensitivity Metabolism and nutrition disorders: edema,

hyperglycemia and alkaline phosphatase increased

Musculoskeletal and connective tissue disorders: back pain, leg cramps, tenosynovitis, arthritis, tetany, twitching

Nervous system disorders: agitation, anxiety, depression, emotional lability, insomnia, akathisia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertonia, irritability, headache, hyperesthesia

Renal and urinary disorders: hematuria, cystitis, polyuria, urinary frequency, urinary urgency

Reproductive system and breast disorders: miscarriage, dysmenorrhea

Respiratory, thoracic and mediastinal disorders: bronchitis, bronchospasm, epistaxis, hiccup, laryngitis, yawn, apnea, voice alteration

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, angioedema

8.3.1 Less Common Clinical Trial Adverse Reactions - Pediatrics

There is insufficient data available for the accurate identification of less common clinical trial adverse reactions in pediatric patients.

8.5 Post-Market Adverse 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 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

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 and hypersensitivity reactions, including angioedema, in patients receiving zolmitriptan. There have also been reports of 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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Ergot-Containing Drugs (see 2 CONTRAINDICATIONS; 9.4 Drug-Drug Interactions)
- Other 5-HT_1 Agonists (see 2 CONTRAINDICATIONS; 9.4 Drug-Drug Interactions)
- MAO Inhibitors (see 2 CONTRAINDICATIONS; 9.4 Drug-Drug Interactions)
- Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors (see 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

Due to the potential for additive pharmacodynamic effects, serious drug-drug interactions may occur when NRA-ZOLMITRIPTAN is used concomitantly with ergot-containing or ergot-type medications, increasing the risk of prolonged vasospastic reactions. There is also a potential increased risk of coronary vasospasm with co-administration of other 5-HT1 agonists. The use of NRA-ZOLMITRIPTAN within 24 hours of ergot-containing drugs or other 5-HT1 agonists is contraindicated (see 2 CONTRAINDICATIONS; 9.1 Serious Drug Interactions).

Co-administration of NRA-ZOLMITRIPTAN with other 5-HT1 agonists, monoamine oxidase (MOA) inhibitors, serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) can increase the risk of life-threatening serotonin toxicity/serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS - Neurologic). Concomitant use of NRA-ZOLMITRIPTAN with any of these medications is contraindicated (see 2 CONTRAINDICATIONS; 9.1 Serious Drug Interactions).

Zolmitriptan is metabolized in the liver primarily by CYP1A2 and monoamine oxidase. Drugs that inhibit these enzymes can significantly increase exposure to both zolmitriptan and its active metabolite, N-desmethylzolmitriptan. Patients taking cimetidine and other CYP1A2 inhibitors should not exceed a dose of 5 mg NRA-ZOLMITRIPTAN in any 24 hour period. Co-administration of NRA-ZOLMITRIPTAN with any MAO inhibitor is contraindicated (see 2 CONTRAINDICATIONS).

Propranolol, at a dose of 160 mg/day for 1 week, increased C_{max} and AUC of zolmitriptan by 1.5-fold, while reducing C_{max} and AUC of N-desmethylzolmitriptan by 30% and 15%, respectively. However, there were no changes in the pharmacological effect on blood

pressure or pulse rate.

Retrospective analysis of pharmacokinetic data across studies indicate that oral contraceptives increase mean C_{max} and AUC of zolmitriptan by 30% and 50%, respectively and delay T_{max} by 30 minutes. Effects of zolmitriptan on the pharmacokinetics of oral contraceptives has not been studied.

Constituents in St. John's Wort possess high potency in the inhibition of CYP enzymes involved in the metabolism of zolmitriptan and use with NRA-ZOLMITRIPTAN should be avoided. Green tea extract is a mild inhibitor of CYP1A2 and its use with NRA-ZOLMITRIPTAN should be limited.

Smoking and alcohol consumption may increase the risk of serious cardiac adverse events (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Zolmitriptan does not induce or inhibit cytochrome P450 enzymes and is unlikely to affect clearance of drugs metabolized by these enzymes.

9.3 Drug-Behavioural Interactions

Smoking or tobacco use may increase the risk of serious cardiac events (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Alcohol use can increase the risk of certain central nervous system adverse events, including dizziness, somnolence, and abnormal thinking. The use of alcohol should be avoided or limited during treatment with NRA-ZOLMITRIPTAN. Interaction studies were performed with caffeine and found no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interaction

Drug name/Class	Source of Evidence	Effect	Clinical comment
Ergot-containing Drugs (e.g. dihydroergotamine, ergotamine, methysergide)	T, C	Potential additive pharmacodynamic effects, causing prolonged vasospastic reactions.	The use of NRA-ZOLMITRIPTAN within 24 hours of ergot-containing or ergot-type medications is contraindicated (see 2 CONTRAINDICATIONS).

Drug name/Class	Source of Evidence	Effect	Clinical comment
Other 5-HT1 Agonists (e.g. sumaptriptan, rizatriptan, almotriptan, eletriptan, naratriptan, frovatriptan)	T	Potential additive effect, increasing the risk of coronary vasospasm. Potential risk of serotonin toxicity/serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS -Neurologic).	Use of NRA-ZOLMITRIPTAN within 24 hours of other 5-HT1 agonists is contraindicated (see 2 CONTRAINDICATIONS).
MAO-A Inhibitors (e.g. clorgyline, moclobemide)	CT	Increased exposure (26% increase in both AUC and C_{max} for zolmitriptan and a 3-fold increase in the AUC and C_{max} of the active metabolite N- desmethylzolmitriptan). Potential risk of serotonin toxicity/serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS -Neurologic).	NRA-ZOLMITRIPTAN is contraindicated in patients taking **any** MAO inhibitor (see 2 CONTRAINDICATIONS).
MAO-B Inhibitors (e.g. selegiline, rasagiline)	CT	No effect on the pharmacokinetic parameters of zolmitriptan or the active metabolite, N-desmethylzolmitriptan.	The specificity of MAO-B inhibitors, such as selegiline, diminishes with higher doses and varies between patients. NRA-ZOLMITRIPTAN is contraindicated in patients taking **any** MAO inhibitor (see 2 CONTRAINDICATIONS).
Cimetidine and other CYP1A2 Inhibitors (e.g. fluvoxamine, ciprofloxacin)	CT	2-fold increase in exposure to both zolmitriptan and its active metabolite, N-desmethylzolmitriptan	Patients taking cimetidine or specific inhibitors of CYP1A2 should not exceed a dose of 5 mg NRA-ZOLMITRIPTAN in any 24 hour period.
Oral Contraceptives	CT	Increased exposure to zolmitriptan (30% higher C_{max} and 50% higher AUC) and delayed T_{max}. Effects of zolmitriptan on oral contraceptives have not been determined.	No dosage adjustment is required.

Drug name/Class	Source of Evidence	Effect	Clinical comment
Propranolol	CT	1.5-fold increase in zolmitriptan exposure	There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan. No dosage adjustment required.
Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, sertraline, paroxetine) Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (e.g. duloxetine, venlafaxine)	CT, T	Cases of life-threatening serotonin toxicity/ serotonin syndrome have been reported during combined use of SSRIs or SNRIs and triptans (see 7 WARNINGS AND PRECAUTIONS - Neurologic)	NRA-ZOLMITRIPTAN is contraindicated in patients taking SSRIs or SNRIs (see 2 CONTRAINDICATIONS).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

No clinically significant pharmacokinetic interactions were observed when zolmitriptan was co-administered with acetaminophen, metoclopramide, rifampicin, or xylometazoline

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions of zolmitriptan with herbal products have not been studied.

St John's Wort: Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's wort (Hypericum perforatum). Concomitant use of NRA-ZOLMITRIPTAN with St John's Wort should be avoided.

Green tea: Green tea extracts are mild inhibitors of CYP1A2 enzymes. The ingestion of green tea extract or its associated catechins is not expected to result in clinically significant influences on zolmitriptan exposure. However, some caution is advised in the consumption of excessive amounts of green tea beverages or green tea extract in patients prescribed NRA-ZOLMITRIPTAN.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 (N- desmethylzolmitriptan) 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-HT1B/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.

10.2 Pharmacodynamics

In clinical studies, the proportion of patients with undesirable effects has been shown to increase with increasing dose.

The remaining pharmacodynamic data was obtained from nonclinical studies.

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 humans results in the formation of a pharmacologically active N- demethylated derivative (see 10.3 Pharmacokinetics). 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.

10.3 Pharmacokinetics

Table 5 - Summary of Zolmitriptan Tablets Pharmacokinetic Parameters in Healthy Volunteers**

Formulation	Cmax (ng/mL)	Tmax (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng.h/mL)	CL* (L/hour)	Vd L/kg
Zolmitriptan Tablets 2.5 mg	3	2	2.58	17	183	7

* systemic clearance

** parameters may vary slightly in migraineurs

Zolmitriptan Tablets

Absorption: In human, 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.

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: Metabolism of zolmitriptan is dependent on CYP1A2 and the metabolism of the active metabolite N-desmethylzolmitriptan is via the monoamine oxidase A (MAOA) enzyme system. The enzymes responsible for the metabolism of zolmitriptan remain to be fully characterized.

Conversion of zolmitriptan to the active metabolite N-desmethylzolmitriptan occurs such that metabolite concentrations are approximately two thirds that of zolmitriptan. Because the 5-$HT_{1B/1D}$ potency of N-desmethylzolmitriptan 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 N- desmethylzolmitriptan is 3 hours and the T_{max} is approximately 2 to 3 hours.

Elimination: Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. 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 metabolite N-desmethylzolmitriptan accounted for 4% of the dose.

Special Populations and Conditions

- **Pediatrics (<12 years of age):** Zolmitriptan pharmacokinetics have not been established in children under the age of 12 years.

- **Pediatrics (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. The metabolite is 2 to 6 times more potent at 5- HT1D receptors (see 10.2 Pharmacodynamics).
- **Geriatrics:** Zolmitriptan pharmacokinetics in healthy elderly non-migraineur (non-migraine sufferers) volunteers (65-76 years of age) were similar to those in younger non-migraineur volunteers (18-39 years of age).
- **Sex:** Mean plasma concentrations of zolmitriptan were up to 1.5-fold greater in females than in males.
- **Pregnancy and Breast-feeding:** Zolmitriptan has not been studied in pregnant or breast- feeding women. Resulting exposures to the fetus, neonate, or infant have not been determined (see 7.1 Special Populations).
- **Ethnic Origin:** 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 metabolite N-desmethylzolmitriptan, was decreased. For N-desmethylzolmitriptan, 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 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 N-desmethylzolmitriptan 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 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic; 4.1 Dosing Considerations).
- **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).
- **Obesity:** Zolmitriptan pharmacokinetics in obese patients have not been established.
- **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. NRA-ZOLMITRIPTAN is contraindicated in patients with uncontrolled or severe hypertension (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

11 STORAGE, STABILITY AND DISPOSAL

NRA-ZOLMITRIPTAN tablets should be stored at room temperature between 15°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements for handling.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

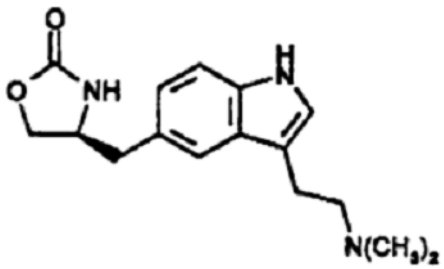
Drug Substance

Proper 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 g/mol

Structural formula:



Physicochemical 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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication: Acute Treatment Of Migraine Attacks, With Or Without Aura, In Adults

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 Tablets

Table 6 - Summary of patient demographics for clinical trials in the acute treatment of migraine attacks, with or without aura, in adults using Zolmitriptan Tablets

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
136-006	single centre, double–blind, placebo-controlled dose finding study	single dose: 1 mg, 5 mg, or placebo; oral; within 6 hours of headache onset optional second dose: 15 mg, 20 mg, or 10 mg; oral; 2 hours following the first dose	Patients with a diagnosis of migraine with or without aura placebo: n=20 1 mg: n=22 5 mg: n=21	Mean N/A* (20-54)	Males (20%)
136-008	multi-centre randomized, double blind, placebo-controlled, parallel group, dose range finding study	single dose: 5-20 mg; oral; within 6 hours of headache onset or waking with the headache	Patients with a diagnosis of migraine with or without aura placebo: n=99 5 mg: n=213	Mean N/A* (18-66)	Males (16%)
136-017	multicenter, double–blind, randomized, placebo–controlled, parallel group study	1 or 2.5 or 5 or 10 mg oral within 12 hours of headache onset or waking up with headache. optional second dose: same as initial dose was possible within 4 to	Patients with a diagnosis of migraine with or without aura placebo: n=140 1 mg: n=141 2.5 mg: n=298 5 mg: n=280	Mean N/A* (12-65)	Males (12%)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
		24 hours after initial dose			
136018	multicentre, double-blind, placebo-controlled	single dose: placebo or 5 mg zolmitriptan; oral; within 6 hours of headache onset or waking with the headache optional second dose: 2 hours following the first dose	placebo: n=56 5 mg : n=498	Mean N/A* (18-65)	**placebo** Males: (14%) **zolmitriptan** Males: (17%)
136-042	multicenter, double–blind, randomized, placebo–controlled study	2.5 mg; oral; within 12 hours of headache onset or waking with a headache	placebo: n=108 zolmitriptan: n=219	Mean N/A* (12–65)	Males (15%)

* Mean age is not available.

The efficacy of zolmitriptan 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 7 Percentage of Patients with Pain Relief (1/0)♦ at 2 Hours - Intent to Treat Population

Study	Hour Post-dose	Placebo	Zolmitriptan Tablets Dose (mg)		
			1	2.5	5
		%	%	%	%
136-006	2	15 (N=20)	27 (N=22)	-	62† (N=21)
136-008	2	21 (N=99)	-	-	61 (N=213)
136-017	2	32 (N=140)	50† (N=141)	63†** (N=298)	65†** (N=280)
136-018	2	44 (N=56)	-	-	59 (N=498)
136-042	2	36 (N=101)	-	62† (N=200)	-

* $p \leq 0.05$ in comparison with placebo

** $p \leq 0.01$ in comparison with 1 mg

† $p \leq 0.01$ 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)

Table 7 shows efficacy results for zolmitriptan 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 tablets 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.

The proportion of patients being pain free at 2 hours was statistically significantly greater for patients receiving zolmitriptan 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 tablets 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 tablets dose or other medication for migraine over 24 hours following the initial dose of study treatment was lower for zolmitriptan tablets 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.

14.2 Comparative Bioavailability Studies

A randomized, double-blinded, single dose, two-way, crossover, comparative bioavailability study of NRA-ZOLMITRIPTAN 2.5 mg tablets (Nora Pharma Inc .) with ZOMIG® 2.5 mg tablets (AstraZeneca Canada Inc.) was conducted in 25 healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 25 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Zolmitriptan (1 x 2.5 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg·h/mL)	32546.02 34903.77 (38.29)	30532.56 32680.96 (36.62)	107.0	101.1 – 113.1
AUC_I (pg·h/mL)	33857.69 36208.20 (37.31)	31773.54 33932.34 (35.93)	106.9	101.5 – 112.6
C_{max} (pg/mL)	6138.57 6550.23 (37.97)	5841.55 6399.85 (43.16)	105.9	95.4 – 117.6
T_{max}[3] (h)	1.50 (0.75 – 5.00)	1.25 (0.50 – 5.00)		
$T_{½}$[4] (h)	3.41 (29.42)	3.44 (32.88)		

[1] NRA-ZOLMITRIPTAN (zolmitriptan) tablets, 2.5 mg (Nora Pharma Inc .)

[2] ZOMIG® (zolmitriptan) tablets, 2.5 mg (AstraZeneca Canada Inc.)

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Genotoxicity: 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.

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.

Reproductive and Developmental Toxicology: Reproductive studies in male and female rats, at dose levels limited by toxicity, revealed no effect on fertility or reproduction. Evaluation of experimental animal studies does not indicate direct teratogenic effects. However, some findings in embryotoxicity studies suggested impaired embryo viability

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 .

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.

Juvenile Toxicity: No dedicated juvenile toxicity studies have been performed for zolmitriptan.

Special Toxicology: 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ZOMIG® (tablets, 2.5 mg), ZOMIG RAPIMELT® (orally disintegrating tablets, 2.5 mg), ZOMIG® NASAL SPRAY (spray, 2.5 mg and 5 mg), control 273863, Product Monograph, Xediton Pharmaceuticals Inc. (APR 25, 2024)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]NRA-ZOLMITRIPTAN
zolmitriptan tablets

Read this carefully before you start taking **NRA-ZOLMITRIPTAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NRA-ZOLMITRIPTAN**.

Serious Warnings and Precautions

- **Risk of Heart Attack:** Serious heart events including heart attack have been reported within a few hours of starting treatment with NRA-ZOLMITRIPTAN. Do NOT use this medication if you have any form of coronary artery disease.
- **Heart Rhythm Problems:** Life-threatening instances of heart rhythm disturbances have been reported within a few hours of starting treatment with NRA-ZOLMITRIPTAN. This can be fatal.
- **Chest Pain:** NRA-ZOLMITRIPTAN may cause chest pain, even in patients without a history of coronary artery disease.
- **Risk of Stroke:** Bleeding in the brain and stroke have been reported in patients taking medications like NRA-ZOLMITRIPTAN. These conditions can be fatal.

If you think you are experiencing any of the above, contact your healthcare professional or get immediate medical help.

What is NRA-ZOLMITRIPTAN used for?

NRA-ZOLMITRIPTAN is used in adults to relieve migraine headache and other associated symptoms of a migraine attack.

NRA-ZOLMITRIPTAN should not be used to prevent or reduce the number of attacks you experience. Only use NRA-ZOLMITRIPTAN to treat an actual migraine headache attack.
How do NRA-ZOLMITRIPTAN work?

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

What are the ingredients in NRA-ZOLMITRIPTAN?

NRA-ZOLMITRIPTAN:

Medicinal ingredients: zolmitriptan.

Non-medicinal ingredients: anhydrous lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and the Film Coating ingredients containing the following: Hypromellose, Polyethylene glycol, Titanium dioxide and Yellow iron oxide.

NRA-ZOLMITRIPTAN comes in the following dosage forms:

NRA-ZOLMITRIPTAN: tablets, 2.5 mg.

Do not use NRA-ZOLMITRIPTAN if:

- you are allergic to zolmitriptan or any of the other ingredients in NRA-ZOLMITRIPTAN (see "What are the ingredients in NRA-ZOLMITRIPTAN?")
- you have a history, or any signs or symptoms of a heart problem or condition
- you have ever had a heart attack or stroke
- you suffer from chest pain, occurring either on exertion or at rest
- you have severe or uncontrolled hypertension
- you are taking or have recently taken (within the last 24 hours) an ergotamine containing or ergot-like drug, or another triptan used to treat migraines
- you are taking or have recently taken (within 2 weeks) a monoamine oxidase inhibitor (MAOI)
- you have another type of headache, that is different from a migraine attack (if you are not sure, ask your healthcare professional. These include:
    - Hemiplegic migraines: these are migraine headaches where you have weakness on one side of your body.
    - Basilar migraines: these are migraine headaches that start in the lower part of the brain.
    - Ophthalmoplegic migraines: these are migraine headaches where you have pain around the eyes.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NRA-ZOLMITRIPTAN. Talk about any health conditions or problems you may have, including if you:

- have any liver problems
- are at risk of developing heart disease, risk factors include if you:
    - have high blood pressure
    - have high cholesterol
    - are obese
    - have diabetes
    - have a family history of heart disease
    - are a smoker
    - are a postmenopausal female
    - are a male over 40 years of age
- have a condition called Wolff-Parkinson-White syndrome

- have any other allergies or sensitivities
- have a history of epilepsy or structural brain lesions
- have a history of drug use
- are pregnant, think you are pregnant or are planning to become pregnant
- are breastfeeding, or plan to breastfeed
- are over 65 years of age
- have a rare hereditary galactose intolerance such as Lapp lactase deficiency or glucose-galactose malabsorption, because NRA-ZOLMITRIPTAN tablets contain lactose

Other warnings you should know about:

Driving and Using Machines: NRA-ZOLMITRIPTAN can cause sedation. Avoid driving or using machines until you know how the medication affects you.

Overuse of NRA-ZOLMITRIPTAN: As with other migraine treatments, using too much NRA-ZOLMITRIPTAN can cause daily headaches or make your migraine headaches worse. Ask your healthcare professional if you think this is the case for you. You may need to stop using NRA-ZOLMITRIPTAN to correct the problem.

Risk of Eye Problems: Long-term use of NRA-ZOLMITRIPTAN may cause eye problems. If you develop any problems with your eyes, tell your healthcare professional **right away**.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do NOT take NRA-ZOLMITRIPTAN if you are taking or have taken:

- In the last 24 hours, any medications that contain ergotamine (such as dihydroergotamine, methysergide).
- In the last 24 hours, other medications like NRA-ZOLMITRIPTAN (such as sumatriptan, naratriptan, almotriptan, rizatriptan or eletriptan).
- Within the last 2 weeks, a monoamine oxidase inhibitor (MAOI) (such as phenelzine sulfate, tranylcypromine sulfate, moclobemide).
- Any selective serotonin reuptake inhibitors (SSRI's) such as fluoxetine, sertraline, fluvoxamine, paroxetine, or any serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine hydrochloride. These medications are often used in the treatment of depression.

The following may interact with NRA-ZOLMITRIPTAN:

- medicines used to treat upset stomach or stomach ulcers (such as cimetidine)
- antibiotics from the quinolone family (such as ciprofloxacin)
- oral contraceptives
- propranolol, a beta blocker used to treat heart rhythm problems
- smoking or tobacco
- alcohol
- excessive amounts of green tea or green tea extract
- herbal remedies containing St John's wort

How to take NRA-ZOLMITRIPTAN:

- Take NRA-ZOLMITRIPTAN exactly as your healthcare professional has told you to.

Usual dose:

NRA-ZOLMITRIPTAN Tablets:

- The usual starting dose is 2.5 mg at the first sign of a migraine attack.
- Swallow the tablet with water.
- If your healthcare professional has recommended a smaller dose for you, the tablet can be broken in half.

If your headache returns and it has been at least 2 hours since you took your first dose, you may take a second dose. The maximum dose is 10 mg in any 24 hour period. If your first dose did not relieve your migraine headache, do not take a second dose without talking to your healthcare professional first.

Overdose:

If you think you, or a person you are caring for, have taken too much **NRA-ZOLMITRIPTAN**, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

What are possible side effects from using NRA-ZOLMITRIPTAN?

These are not all the possible side effects you may have when taking NRA-ZOLMITRIPTAN. If you experience any side effects not listed here, tell your healthcare professional.

- feeling sick
- vomiting
- dizziness
- tiredness
- weakness
- muscle aches and pains
- difficulty swallowing

- dry mouth
- headache
- stomach pain
- increase in the production of urine or in the frequency of urination

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
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			
Fast heart rate		✓	
Temporary increase in blood pressure		✓	
RARE			
Allergic reaction: shortness of breath, sudden wheeziness, chest tightness, swelling of the eyelids, face, lips, mouth, tongue or neck, lumpy skin rash, or hives			✓
VERY RARE			
Sudden or severe abdominal pain or bloody diarrhea			✓
Symptoms of a heart attack: chest pain, sweating, shortness of breath			✓
UNKNOWN FREQUENCY			
Serotonin toxicity: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38 °C), or rigid muscles.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

NRA-ZOLMITRIPTAN: Store between 15°C and 30°C.
Do not take your medication after the expiry date on the package and blister foil.
If you have any leftover medication that you do not need or is expired, return the tablets to your pharmacist for disposal.

Keep out of reach and sight of children.

If you want more information about NRA-ZOLMITRIPTAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug- product-database.html); or by calling 1-888 270-9874.

This leaflet was prepared by Nora Pharma

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