

PRODUCT MONOGRAPH

^{Pr}TEVA-RIZATRIPTAN

rizatriptan benzoate tablets
5 mg and 10 mg rizatriptan (as rizatriptan benzoate)

5-HT₁ Receptor Agonist

Migraine Therapy

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	10
DRUG INTERACTIONS	15
DOSAGE AND ADMINISTRATION.....	17
OVERDOSAGE	18
ACTION AND CLINICAL PHARMACOLOGY	19
STORAGE AND STABILITY.....	21
DOSAGE FORMS, COMPOSITION AND PACKAGING	21
PART II: SCIENTIFIC INFORMATION	22
PHARMACEUTICAL INFORMATION.....	22
CLINICAL TRIALS.....	23
DETAILED PHARMACOLOGY	25
TOXICOLOGY	28
REFERENCES	30
PART III: CONSUMER INFORMATION.....	31

TEVA-RIZATRIPTAN
as rizatriptan benzoate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablets 5 mg , 10 mg	<i>Lactose monohydrate</i> <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Adults

TEVA-RIZATRIPTAN (rizatriptan benzoate) is indicated for:

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

TEVA-RIZATRIPTAN is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of rizatriptan benzoate has not been established for cluster headache, which is present in an older, predominantly male population.

Pediatrics (<18 years of age)

The safety and efficacy of rizatriptan benzoate has not been established in patients under 18 years of age and its use in this age group is not recommended (see WARNINGS AND PRECAUTIONS).

Geriatrics (> 65 years of age)

The safety and effectiveness of rizatriptan benzoate has not been adequately studied in individuals over 65 years of age. Its use in this age group is, therefore, not recommended (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

TEVA-RIZATRIPTAN (rizatriptan benzoate) 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 rizatriptan benzoate. 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).

Because rizatriptan benzoate may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS AND PRECAUTIONS).

Rizatriptan benzoate is contraindicated within 24 hours of treatment with another 5-HT₁ agonist or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

Rizatriptan benzoate is contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see DRUG INTERACTIONS).

Because there are no data available, rizatriptan benzoate is contraindicated in patients with severe hepatic impairment.

TEVA-RIZATRIPTAN is contraindicated in patients who are hypersensitive to rizatriptan or any component of the formulation.

WARNINGS AND PRECAUTIONS

General

TEVA-RIZATRIPTAN should only be used where a clear diagnosis of migraine has been established.

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Psychomotor Effect

Dizziness, somnolence and asthenia/fatigue were experienced by some patients in clinical trials with rizatriptan benzoate (see ADVERSE EVENTS). Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that rizatriptan benzoate does not adversely affect them.

Cardiovascular

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events
rizatriptan benzoate has been associated with transient chest and/or neck pain and tightness

which may resemble angina pectoris. Following the use of other 5-HT₁ agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of other 5-HT₁ agonists, and may therefore also occur with rizatriptan benzoate. Because of the potential of this class of compounds (5-HT_{1B/1D} agonists) to cause coronary vasospasm, TEVA-RIZATRIPTAN should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that TEVA-RIZATRIPTAN not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, TEVA-RIZATRIPTAN should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of rizatriptan 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 on the first occasion of use an electrocardiogram (ECG) during the interval immediately following TEVA-RIZATRIPTAN, in these patients with risk factors. 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 rizatriptan benzoate who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluation as they continue to use rizatriptan benzoate.

If symptoms consistent with angina occur after the use of TEVA-RIZATRIPTAN, 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 rizatriptan benzoate.

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of rizatriptan. Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and

similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following TEVA-RIZATRIPTAN administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Cardiac Events and Fatalities Associated with 5-HT₁ Agonists

Rizatriptan benzoate 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 5-HT₁ agonists. Considering the extent of use of 5-HT₁ agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience with Rizatriptan Benzoate

Among the approximately 4200 patients who were treated with at least a single oral dose of either 5 or 10 mg rizatriptan in premarketing clinical trials of rizatriptan, electrocardiac adverse experiences were observed in 33 patients. One patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Postmarketing Experience with Rizatriptan Benzoate

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

Cerebrovascular Events and Fatalities Associated with 5-HT₁ Agonists

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT₁ agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with TEVA-RIZATRIPTAN 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, hemorrhage, transient ischemic attack).

Special Cardiovascular Pharmacology Studies with Another 5-HT₁ Agonist

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT₁ agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and one 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 hyperemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT₁ agonist is not known.

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

Other Vasospasm-Related Events

5-HT₁ agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of another 5-HT₁ agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT₁ agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of rizatriptan benzoate (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, TEVA-RIZATRIPTAN should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

Endocrine and Metabolism

Hepatic/Biliary/Pancreatic

Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and DOSAGE AND ADMINISTRATION). Since there are no data in patients with severe hepatic impairment, rizatriptan is contraindicated in this population (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT₁ agonists such as rizatriptan benzoate. 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, rizatriptan benzoate should not be used in patients having a history of hypersensitivity to chemically-related 5-HT₁ receptor agonists.

Neurologic

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

Seizures

Caution should be observed if TEVA-RIZATRIPTAN is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold. There have been very rare reports of seizures following administration of rizatriptan benzoate in patients with or without risk factors or previous history of seizures (see ADVERSE REACTIONS, Post-Marketing Adverse Reactions, Nervous System).

Ophthalmologic

Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin- rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one-year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Renal

Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan, resulting in approximately 44% increase in plasma concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and DOSAGE AND ADMINISTRATION).

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 rizatriptan benzoate and SSRIs (e.g., sertraline, escitalopram oxalate, and fluoxetine) or SNRIs (e.g., venlafaxine, duloxetine) 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).

Special Populations and Conditions

Pregnant Women: In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation. These effects occurred in the absence of any apparent maternal toxicity (maternal plasma drug exposures were 22 and 337 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 20 mg). The developmental no-effect dose was equivalent to 2.25 times human exposure at the MRDD. In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses at the equivalent of 337 times and 168 times, respectively, the human MRDD, during organogenesis. However, fetal weights were decreased in conjunction with decreased maternal weight gain at these same doses. The developmental no-effect dose in both rats and rabbits was 22 times the human MRDD. Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Impairment of Fertility

In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with an equivalent of 337 times the maximum recommended daily dose (MRDD) of 20 mg in humans. The no-effect dose was 22 times the MRDD. There was no impairment of fertility or reproductive performance in male rats treated with up to 825 times the MRDD.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEVA-RIZATRIPTAN is administered to women who are breast-feeding. Rizatriptan is extensively excreted in rat milk, at a level of 5fold or greater than maternal plasma levels.

Pediatrics (< 18 years of age): TEVA-RIZATRIPTAN is not recommended for use in patients under 18 years of age.

In a randomized placebo-controlled trial of 291 adolescent migraineurs, aged 12-17 years, the efficacy of Rizatriptan Benzoate Tablets (5 mg) was not different from that of placebo (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Geriatrics (> 65 years of age): The safety and effectiveness of rizatriptan benzoate has not been adequately 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 with rizatriptan benzoate did not include a substantial number of patients over 65 years of age (n=17). Its use in this age group is, therefore, not recommended.

Special Disease Conditions:

TEVA-RIZATRIPTAN (rizatriptan benzoate) should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Monitoring and Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with TEVA-RIZATRIPTAN.

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT₁ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

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.

**Experience in Controlled Clinical Trials with Rizatriptan Benzoate
Typical 5-HT₁ Agonist Adverse Reactions**

As with other 5-HT₁ agonists, rizatriptan benzoate 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.

Acute Safety

Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of Rizatriptan Benzoate Tablets. The most common adverse events during treatment with rizatriptan benzoate were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose-related. In long-term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Tables 1 and 2 list the adverse events regardless of drug relationship (incidence \geq 1% and greater than placebo) after a single dose of Rizatriptan Benzoate Tablets and Rizatriptan Benzoate Wafers, respectively. Most of the adverse events appear to be dose-related. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected

patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 1: Incidence ($\geq 1\%$ and Greater than Placebo) of Adverse Experiences After a Single Dose of Rizatriptan Benzoate Tablets or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials[†]

	% of Patients		
	Placebo	RIZATRIPTAN BENZOATE 5 mg	RIZATRIPTAN BENZOATE 10 mg
Number of Patients	627	977	1167
Symptoms of Potentially Cardiac Origin			
Upper Limb Sensations*	1.3	1.7	1.8
Chest Sensations*	1.0	1.6	3.1
Neck/Throat/Jaw Sensations*	0.6	1.4	2.5
Palpitations	0.2	0.9	1.0
Body as a Whole			
Asthenia/Fatigue	2.1	4.2	6.9
Abdominal Pain	1.0	1.7	2.2
Digestive System			
Nausea	3.5	4.1	5.7
Dry Mouth	1.3	2.6	3.0
Vomiting	2.1	1.6	2.3
Nervous System			
Dizziness	4.5	4.2	8.9
Somnolence	3.5	4.2	8.4
Headache	0.8	1.8	2.1
Paresthesia	1.0	1.5	2.9
Tremor	1.0	1.3	0.3
Insomnia	0.3	1.0	0.3
Skin and Skin Appendage			
Flushing	1.0	0.6	1.1

* The term “sensations” encompasses adverse events described as pain, discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, weakness and strange sensations.

† Data from Studies 022, 025, 029 and 030.

Table 2: Incidence ($\geq 1\%$ and Greater than Placebo) of Adverse Experiences After a Single Dose of Rizatriptan Benzoate RPD Wafers or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials[†]

	% of Patients		
	Placebo	Rizatriptan Benzoate RPD 5 mg	Rizatriptan Benzoate RPD 10 mg
Number of Patients	283	282	302
Symptoms of Potentially Cardiac Origin			
Chest Sensations*	0.4	1.4	1.7
Neck/throat/Jaw Sensations*	0.4	1.4	2.0
Tachycardia	1.1	1.4	0.3
Upper Limb Sensations*	0.4	0.7	2.0
Palpitations	0.4	0.4	1.0
Body as a Whole			
Asthenia/Fatigue	0.4	2.1	3.6
Digestive System			
Dry Mouth	2.1	6.4	6.0
Nausea	5.7	6.4	7.0
Dyspepsia	0.7	1.1	2.0
Acid Regurgitation	0	1.1	0.7
Salivation Increase	0	0	1.3
Musculoskeletal System			
Regional Heaviness	0	0	1.0
Nervous System			
Dizziness	3.9	6.4	8.6
Somnolence	2.8	4.3	5.3
Headache	0.7	1.8	2.0
Insomnia	0	1.4	0.7
Paresthesia	0.4	1.4	3.0
Hypoesthesia	0	1.4	0.7
Mental Acuity Decreased	0	1.1	0.3
Tremor	0.7	1.1	0
Nervousness	0.4	1.1	0.7
Respiratory System			
Pharyngeal Discomfort	0	1.1	0.7
Skin and Skin Appendage			
Sweating	0.7	1.1	1.0
Special Senses			
Taste Perversion	1.1	1.4	2.3
Blurred Vision	0	0.4	1.3

* The term "sensations" encompasses adverse events described as pain, discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, weakness and strange sensations.

† Data from Studies 039 and 049.

Rizatriptan benzoate was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. The incidences of adverse experiences were not affected by age, gender or use of prophylactic medications. There were insufficient data to assess the impact of race on the incidence of adverse events.

Long-Term Safety

In long-term extension studies, a total of 1854 patients treated 16,150 migraine attacks with Rizatriptan Benzoate 5 mg Tablets and 24,043 attacks with Rizatriptan Benzoate 10 mg Tablets over a period of up to 1 year. In general, the types of clinical adverse experiences observed in the extension studies were similar to those observed in the acute studies. However, the incidences of most clinical adverse events were approximately 3-fold higher in extension, as expected, based on increased observation time. The most common adverse events per attack (defined as occurring at an incidence of at least 1%) for rizatriptan benzoate 5 mg and 10 mg, respectively, were as follows: nausea (3%, 4%), dizziness (2%, 2%), somnolence (2%, 4%), asthenia/fatigue (2%, 2%), headache (1%, 2%), vomiting (1%, <1%), chest pain (<1%, 1%) and paresthesia (<1%, 2%). Due to the lack of placebo controls in the extension studies, the role of rizatriptan benzoate causation cannot be reliably determined.

Other Events Observed in Association with the Administration of Rizatriptan Benzoate

In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of rizatriptan benzoate 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 Rizatriptan Benzoate 5 mg and 10 mg tablets in Phase II and III studies (n=3716) and reported an event divided by the total number of patients exposed to rizatriptan benzoate. 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 using the following definitions: frequent adverse events are those defined as those occurring in at least 1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

Body as a Whole

Frequent were warm sensations, chest pain and chills/cold sensations. Infrequent were heat sensitivity, facial edema, hangover effect, abdominal distention, edema/swelling and malaise. Rare were fever, orthostatic effects, and syncope.

Cardiovascular

Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare were angina pectoris and blood pressure increased.

Digestive

Frequent was diarrhea. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), eructation and glossodynia.

Metabolic

Infrequent was dehydration.

Musculoskeletal

Infrequent were muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, and arthralgia.

Neurological/Psychiatric

Frequent were hypoesthesia and mental acuity decreased. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, euphoria, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation, hyperesthesia, sleep disorder, speech disorder, migraine and spasm. Rare were dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory

Frequent were dyspnea and pharyngeal discomfort. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion, dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses

Frequent was taste perversion. Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage

Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital System

Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported very rarely and most have been reported in patients with risk factors predictive of CAD: Myocardial ischemia or infarction, cerebrovascular accident.

The following adverse reactions have also been reported:

Hypersensitivity: Hypersensitivity reaction, anaphylaxis/anaphylactoid reaction, angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, urticaria, rash, toxic epidermal necrolysis.

Nervous System: serotonin syndrome.

Seizures: There have been very rare reports of seizures following administration of rizatriptan benzoate in patients with or without risk factors or previous history of seizures (see WARNINGS AND PRECAUTIONS).

Musculoskeletal: facial pain.

Special Senses: Dysgeusia.

Vascular disorders: Peripheral vascular ischemia

Gastrointestinal Disorders: Ischemic colitis

Drug Abuse and Dependence

Although the abuse potential of rizatriptan benzoate has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received rizatriptan benzoate in clinical trials or their extensions. The 5-HT^{1B/1D} agonists, as a class, have not been associated with drug abuse.

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 that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Monoamine Oxidase Inhibitors

Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). In a drug interaction study, when rizatriptan benzoate 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41%, respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. Drug interaction studies were not conducted with selective MAO-B inhibitors. The specificity of MAO-B inhibitors diminishes with higher doses and varies among patients. Therefore, co-

administration of rizatriptan in patients taking MAO-A or MAO-B inhibitors is contraindicated (see CONTRAINDICATIONS).

Nadolol/Metoprolol

In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Oral Contraceptives

In a study of concurrent administration of an oral contraceptive during 6 days of administration of rizatriptan benzoate (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Other 5-HT₁ Agonists

The administration of rizatriptan with other 5-HT₁ agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, co-administration of rizatriptan and other 5-HT₁ agonists within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

Propranolol

Rizatriptan benzoate should be used with caution in patients receiving propranolol, since the pharmacokinetic behavior of rizatriptan during co-administration with propranolol may be unpredictable. In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC and C_{max} for rizatriptan were increased by 70% and 75%, respectively, during propranolol administration. In one subject, a 4-fold increase in AUC and 5-fold increase in C_{max} was observed. This subject was not distinguishable from the others based on demographic characteristics. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See DOSAGE AND ADMINISTRATION).

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

Cases of life-threatening serotonin syndrome have been reported in post-marketing experience during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. (See WARNINGS AND PRECAUTIONS.)

In a pharmacokinetic study with paroxetine and rizatriptan, paroxetine had no influence on the plasma levels of rizatriptan.

Drug-Food Interactions

Interactions with food have not been studied. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, Rizatriptan benzoate was administered without regard to food.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

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

Drug-Lifestyle Interactions

Lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TEVA-RIZATRIPTAN (rizatriptan benzoate) is recommended only for the acute treatment of migraine attacks. TEVA-RIZATRIPTAN should not be used prophylactically.

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

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Recommended Dose and Dosage Adjustment

ADULTS

TEVA-RIZATRIPTAN Tablets

The recommended single adult dose is 5 mg. The maximum recommended single dose is 10 mg. There is evidence that the 10 mg dose may provide a greater effect than the 5 mg dose (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies). The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10 mg dose with the potential risk for increased adverse events.

Redosing

Doses should be separated by at least 2 hours; no more than a total of 20 mg should be taken in any 24-hour period.

Patients receiving propranolol

A single 5 mg dose of TEVA-RIZATRIPTAN should be used. In no instances should the total daily dose exceed 10 mg per day, given in two doses, separated by at least two hours (see DRUG INTERACTIONS).

Renal Impairment

In hemodialysis patients with severe renal impairment (creatinine clearance <2 mL/min/1.73 m²), the AUC of rizatriptan was approximately 44% greater than in patients with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). Consequently, if treatment is deemed advisable in these patients, the 5 mg TEVA-

RIZATRIPTAN Tablet should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in renally impaired patients has not been evaluated.

Hepatic Impairment

TEVA-RIZATRIPTAN is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) due to the absence of safety data. Plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). Consequently, if treatment is deemed advisable in the presence of moderate hepatic impairment, the 5 mg TEVA-RIZATRIPTAN Tablet should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in hepatically impaired patients has not been evaluated.

Patients with Hypertension

TEVA-RIZATRIPTAN should not be used in patients with uncontrolled or severe hypertension. In patients with mild to moderate controlled hypertension, patients should be treated cautiously at the lowest effective dose.

OVERDOSAGE

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

No overdoses of rizatriptan benzoate were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25-year-old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with TEVA-RIZATRIPTAN. The elimination half-life of rizatriptan is 2 to 3 hours (see ACTION AND CLINICAL PHARMACOLOGY). Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

There is no specific antidote to rizatriptan. 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.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TEVA-RIZATRIPTAN (rizatriptan benzoate) is a selective 5-hydroxytryptamine_{1B/1D} (5-HT_{1B/1D}) receptor agonist. Rizatriptan binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} receptors. It has weak affinity for other 5-HT₁ receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT₇ receptor, but has no significant activity at 5-HT₂, 5-HT₃, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT_{1B/1D} receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

Absorption: Rizatriptan benzoate is completely absorbed following oral administration. The mean oral absolute bioavailability of the Rizatriptan Benzoate Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, rizatriptan was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

When rizatriptan benzoate 10 mg was administered every 2 hours for three doses on four consecutive days, the plasma concentrations of rizatriptan within each day were approximately 3-fold greater than those seen with a single 10 mg dose and no plasma accumulation of the drug occurred from day to day.

AUC of rizatriptan is approximately 30% higher in females than in males.

Distribution: The mean volume of distribution is approximately 140 liters in male subjects and 110 liters in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

Metabolism: The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-HT_{1B/1D} receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-HT_{1B/1D} receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-HT_{1B/1D} receptor.

Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (K_i=1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations

Excretion: The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ¹⁴C-rizatriptan. Following oral administration of ¹⁴C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Table 3 Pharmacokinetic Parameters of a Single Dose of Rizatriptan in Females (n = 12)

Arithmetic Mean (± SD)				
	Rizatriptan 5 mg Tablet	Rizatriptan RPD 5 mg Tablet	Rizatriptan 10 mg Tablet	Rizatriptan RPD 10 mg Tablet
AUC(0-∞) (ng•hr/mL) ^a	34.5 ± 13.0	33.2 ± 9.8	73.9 ± 23.4	75.9 ± 24.7
C _{max} (ng/mL) ^a	10.4 ± 3.9	11.1 ± 4.7	21.3 ± 6.9	20.3 ± 7.9
T _{max} (hr)	1.0 ± 0.6	1.6 ± 0.8*	1.5 ± 0.8	2.5 ± 1.4*
t _{1/2} (hr) ^b	1.7	1.6	1.7	1.7
Plasma Clearance (mL/min) ^c	1050.5 ± 224.5	1121.2 ± 241.6	1081.6 ± 239.4	1099.3 ± 251.7
a Potency-normalized				
b Harmonic mean				
c Plasma clearance of 1-mg stable, heavy-labeled I.V. dose of rizatriptan given concomitantly with oral dose				
* P < 0.05 compared to tablet formulation				

Special Populations and Conditions

Pediatrics: The mean AUC_{0-∞} and C_{max} of rizatriptan (10 mg orally) were about 12% and 19% higher in adolescents (n=12) as compared to historical data in adults, respectively.

TEVA-RIZATRIPTAN is not recommended for use in patients under 18 years of age (see WARNING AND PRECAUTIONS, Pediatric Use (<18 years of age)). In a single study in adolescents (n=291), there were no significant differences with respect to headache relief at 2 hours between rizatriptan benzoate and placebo treated groups.

Geriatrics: Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender: The mean $AUC_{0-\infty}$ and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Race: Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects. The effect of race on the pharmacokinetics of rizatriptan has not been systematically evaluated.

Hepatic Insufficiency: Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency (see WARNINGS AND PRECAUTIONS). Since there are no data in patients with severe hepatic impairment (Child-Pugh grade C), rizatriptan is contraindicated in this population (see CONTRAINDICATIONS).

Renal Insufficiency: In patients with renal impairment (creatinine clearance 10-60 mL/min/1.73 m²), the $AUC_{0-\infty}$ of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients (creatinine clearance < 2 mL/min/1.73 m²), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function (see WARNINGS AND PRECAUTIONS).

STORAGE AND STABILITY

Tablets

Store the tablets at room temperature (15°C - 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets

Each compressed tablet contains either 5 mg or 10 mg of rizatriptan (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively) and the following non-medicinal ingredients: lactose monohydrate, Sodium Starch Glycolate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

TEVA-RIZATRIPTAN 5 mg are white to off-white, capsule-shaped tablets, engraved with 93 on one side and 7471 the other side. Available in blister packages of 10 and bottles of 50 tablets.

TEVA-RIZATRIPTAN 10 mg are white to off-white, capsule-shaped tablets, engraved with 93 on one side and 7472 the other side. Available in blister packages of 10 and bottles of 50 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

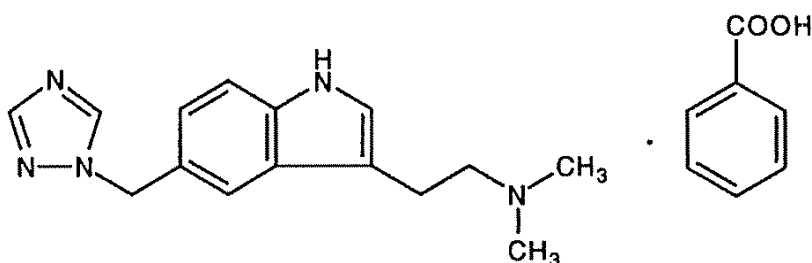
Proper name: rizatriptan benzoate

Chemical name: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate

Molecular formula: $C_{15}H_{19}N_5 \cdot C_7H_6O_2$

Molecular mass: The molecular weight of the benzoate salt is 391.47;
the molecular weight of the free base is 269.4.

Structural formula:



Physicochemical properties:

Description:

Rizatriptan benzoate is a white to off-white, crystalline powder. Rizatriptan benzoate is soluble in water at greater than 3 mg per mL (as dose solubility <250 mL, rizatriptan is considered highly soluble) at 25°C. Rizatriptan benzoate melts at 178 – 180°C.

COMPARATIVE BIOAVAILABILITY DATA

CLINICAL TRIALS

A single-dose crossover comparative bioavailability study between Teva-Rizatriptan 10 mg tablets (Teva Canada Limited, Canada) and MAXALT® 10 mg tablets (Merck Frosst Canada Ltd., Canada) in 30 healthy adult male and female subjects under fasting conditions. Twenty nine (29) subjects were included in the calculation of the presented pharmacokinetic parameters. The Comparative Bioavailability Data for rizatriptan is summarized below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Rizatriptan (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC _T (ng*h/mL)	90.656 93.201 (22)	92.263 94.993 (23)	98.26	94.82 – 101.82
AUC _{inf} (ng*h/mL)	91.572 94.134 (22)	93.167 95.909 (23)	98.29	94.85 – 101.85
AUC _{Reftmax} (ng*h/mL)	10.215 13.836 (76)	12.305 14.669 (58)	83.02	72.77 - 94.72
C _{max} (ng/mL)	27.686 29.014 (29)	28.271 29.190 (26)	97.93	90.54 – 105.92
T _{max} § (h)	0.80 (37)	0.89 (60)		
T _{1/2} § (h)	1.87 (12)	1.86 (12)		

* Rizatriptan benzoate 10 mg Tablets (Teva Canada Limited, Canada)

† Maxalt® 10 mg Tablets (Merck Frosst Canada Ltd., Canada)

§ Expressed as the arithmetic mean (CV%) only

CLINICAL TRIALS

Study results

Rizatriptan Benzoate Tablets

The efficacy of Rizatriptan Benzoate Tablets was established in four multicenter, randomized, placebo-controlled trials. Patients enrolled in these studies were primarily female (84%) and Caucasian (88%), with a mean age of 40 years (range of 18 to 71). Patients were instructed to treat a moderate to severe headache. Headache response (defined as a reduction of moderate or severe headache pain to no or mild headache pain), was assessed for up to 2 hours (Study 1) or up to 4 hours after dosing (Studies 2, 3 and 4). Associated symptoms of nausea, photophobia, and phonophobia and maintenance of response up to 24 hours postdose were evaluated. A second dose of Rizatriptan Benzoate Tablets was allowed 2 to 24 hours after dosing for treatment of recurrent headache in Studies 1 and 2. Additional analgesics and/or antiemetics were allowed 2 hours after initial treatment for rescue in all four studies.

In all studies, the percentage of patients achieving headache response 2 hours after treatment was significantly greater in patients who received either Rizatriptan Benzoate 5 or 10 mg Tablets compared to those who received placebo. In a separate study, doses of 2.5 mg were not different from placebo. Doses greater than 10 mg were associated with an increased incidence of adverse effects. The results from the 4 controlled studies using the marketed formulation are summarized in Table 4.

Table 4 Response Rates¹ 2 Hours Following Treatment of Initial Headache

Study	Placebo	Rizatriptan Benzoate Tablets 5 mg	Rizatriptan Benzoate Tablets 10 mg
1	35% (n=304)	62%* (n=458)	71%*,** (n=456)
2†	37% (n=82)	—	77%* (n=320)
3	23% (n=80)	63%* (n=352)	—
4	40% (n=159)	60%* (n=164)	67%* (n=385)

¹ Pain response is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate pain) to grade 1 or 0 (mild or no pain)

* p value < 0.05 in comparison with placebo

** p value < 0.05 in comparison with 5 mg

† Results for initial headache only

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

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

Efficacy was unaffected by the presence of aura; by the gender, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives. There were insufficient data to assess the impact of race on efficacy.

The long-term efficacy of Rizatriptan Benzoate 5 mg and 10 mg Tablets was investigated in a total of 1854 patients in optional extension phases of three Phase III studies. The extension phases were single blind (except in one study where only 10 mg rizatriptan benzoate was used) and patients were randomized to either 5 mg or 10 mg Rizatriptan Benzoate Tablets or standard care. Approximately 16,150 attacks were treated with rizatriptan benzoate 5 mg and approximately 24,043 with rizatriptan benzoate 10 mg over a period of up to 12 months (median number of attacks treated per patient was approximately 17). Headache response was sustained (as judged by the proportion of attacks treated with rizatriptan benzoate per patient resulting in headache relief).

DETAILED PHARMACOLOGY

Non clinical Pharmacodynamics

In Vitro

Rizatriptan has been shown to be a selective agonist at human 5-HT_{1B} (IC₅₀ 11 nM) and 5-HT_{1D} (IC₅₀ 41nM) receptors with 20-40 fold reduced activity at 5-HT_{1A} receptors using radioligand binding and functional pharmacological bioassays.

Rizatriptan has no significant activity at 5-HT₂ or 5-HT₃ receptor subtypes or at alpha- and betaadrenergic receptors, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Rizatriptan contracted human isolated cerebral (middle meningeal) arteries (EC₅₀ 0.09 micromolar) yet was significantly less potent in contracting human isolated coronary arteries (EC₅₀ 1.0 micromolar) with a 5.6 fold lower maximum response.

Rizatriptan's primary metabolite, indole acetic acid derivative, was devoid of activity at human 5-HT receptors. The minor metabolite, monodesmethyl rizatriptan retained activity at human 5-HT_{1B} (IC₅₀ 19 nM) and 5-HT_{1D} (IC₅₀ 9 nM) receptors. The 6-hydroxytryptamine metabolite of rizatriptan that is found only at low levels in humans had an affinity of IC₅₀ 600nM at α _{2a} and of IC₅₀ 140 nM at α _{2c} adrenergic receptors.

In vivo

Rizatriptan caused dose-dependent vasoconstriction within the carotid artery vascular bed in anesthetized dogs (ED₅₀ 54 μ g/kg I.V.; plasma concentration 16 ng/mL) with selectivity for the craniovasculature since effects were not seen in the coronary artery until high (>137 ng/mL) plasma concentrations were reached. In ferrets rizatriptan caused vasoconstriction in the carotid

artery (ED₅₀ 20 µg/kg I.V.) with no evidence for tachyphylaxis to 3 sequential doses of 15 µg/kg I.V.

Rizatriptan produced a dose-dependent inhibition of dural plasma protein extravasation, dural vasodilatation, and central trigeminal pain signal transmission evoked by electrical stimulation of the trigeminal ganglion or dura mater in anesthetized rats.

Rizatriptan (1.0 mg/kg P.O.; plasma level 317 ng/mL) was free of cardiovascular effects in conscious dogs but at higher doses (5 mg/kg P.O. plasma level 1642 ng/mL) produced increases in blood pressure (~ 40 mmHg) and heart rate (~ 80 beats/min) and behavioural activation that were sustained for at least 120 minutes.

Rizatriptan caused a 12% increase in mean arterial blood pressure (mmHg) and a 16% decrease in heart rate (beats/min) with lengthening of the P-R interval (90-103 msec) in anesthetized dogs. QT intervals were unchanged.

Rizatriptan prevented the increases in blood pressure evoked in pithed rats and guinea pigs by stimulation of vascular pre-ganglionic sympathetic nerves.

Rizatriptan caused increases in urine flow (0.46 to 0.83 mL/min), sodium (56-110 microEq/min) and potassium (28-40 microEq/min) excretion in conscious dogs. Average glomerular filtration and effective renal plasma flow rates were unchanged.

Rizatriptan caused behavioural activation and mydriasis at doses >2 mg/kg P.O.

Rizatriptan, in conscious rhesus monkeys, caused behavioral activation and emesis at plasma levels of 260 ng/mL. Rizatriptan (7 mg/kg S.C.) caused mild hypothermia and emesis in squirrel monkeys at high plasma levels of 1546 ng/mL.

Animal Pharmacokinetics

The absorption of oral solutions of rizatriptan in rats and dogs was rapid and high. The time to reach the maximum plasma concentration was 71 minutes in rats and 26 minutes in dogs. The absorption, as measured by the relative urinary excretion of total radioactivity (drug and metabolites) after oral and intravenous doses, was 78% in rats and essentially complete in dogs. The oral bioavailability, as estimated by comparison of plasma AUC_{0-∞} of rizatriptan after oral and intravenous doses, was 64% in rats and 47% in dogs. The apparent discrepancy in the absorption and bioavailability of rizatriptan is consistent with moderate first-pass metabolism of the drug.

The pharmacokinetics of rizatriptan were generally similar in rats and dogs. Plasma concentrations of rizatriptan declined biexponentially with terminal half-lives of 65 minutes in rats and 72 minutes in dogs. The plasma clearance was rapid in rats (71 mL/min/kg) and dogs (46 mL/min/kg). The steady state volumes of distribution were 4.3 L/kg in rats and 3.2 L/kg in dogs. The systemic exposure of rizatriptan increased slightly greater than proportionally with increases in oral doses in rats (3 and 10 mg/kg) and dogs (1, 2 and 5 mg/kg).

Radioactivity was distributed widely throughout the body after a single 3 mg/kg oral or intravenous dose of ¹⁴Crizatriptan in rats. In general, the pattern of distribution was similar after both routes of administration. Tissues with significant percentages of dose were the liver, kidney, small intestine and stomach, while the brain contained only a trace amount of radioactivity. At 24 hours, tissue concentrations of rizatriptan equivalents had declined to trace levels except in organs involved in elimination (i.e., liver, kidney and the G.I. tract). Over a 24-hour period, the recoveries of radioactivity in the G.I. contents and excreta were 85% and 96% of I.V. and oral doses, respectively.

Toxicokinetic studies demonstrated high placental transfer of rizatriptan in pregnant rats and rabbits and high milk transfer in lactating rats (see TOXICOLOGY, Reproduction).

Rizatriptan was poorly bound to plasma proteins of mouse, rat, rabbit, dog and human and the binding was independent of concentration in the range 50-5000 ng/mL. The unbound fraction was 81% in mouse, 82% in rat, 73% in rabbit, 88% in dog and 86% in human.

The pathways of rizatriptan metabolism in laboratory animals (rat, mouse, rabbit, dog) are similar to those in humans, and consist of oxidative deamination, aromatic hydroxylation followed by sulfation, N-oxidation and N-demethylation.

In general, there were no major differences in the qualitative metabolism of rizatriptan in rodents and humans with respect to dosing frequency (single or multiple oral doses), the size of the dose (therapeutically relevant or toxicological doses) or sex. The extent of metabolism, however, was species dependent. Rizatriptan and its metabolites were eliminated primarily via renal excretion, although biliary excretion also played a role in rats. Rizatriptan underwent more extensive metabolism in dogs and humans when compared to two rodent species, less than 15% of oral doses being excreted in urine as the unchanged drug. The indole acetic acid derivative of rizatriptan was the most prominent metabolite in all species studied although the N-oxide analog also was a significant metabolite in rats and dogs.

In rats, both urinary and biliary routes contributed to the elimination of rizatriptan and its metabolites, while in dogs and human, renal excretion was the primary route of elimination. Accordingly, the excretion of an intravenous dose of rizatriptan in rats was 58% in urine and 23% in feces, while that of the oral dose was balanced evenly between urine (45%) and feces (42%). Approximately one-half (I.V.) and one-third (p.o.) of the urinary radioactivity represented rizatriptan while the remainder was divided among several metabolites. In dogs, 75% of oral and intravenous doses was excreted in urine and 12-13% in feces. The majority of urinary radioactivity after either route of administration represented metabolites while the unchanged drug accounted for approximately 7% (p.o.) and 21% (I.V.) of the radioactivity.

Human Pharmacodynamics

In healthy young male and female subjects who received maximal doses of Rizatriptan Benzoate Tablets (10 mg every 2 hours for three doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. These small, transient increases in blood pressure were not clinically significant.

During long-term monitoring of migraine patients in controlled studies, no consistent effects on blood pressure or heart rate were observed.

In a study in healthy male subjects, Rizatriptan Benzoate Tablets 10 mg produced slight, transient peripheral vasoconstriction (measured as a 5.1 mmHg increase in toe-arm systolic blood pressure gradient).

In contrast, intravenous ergotamine (0.25 mg) produced a 14.6 mmHg increase in toe-arm systolic blood pressure gradient. When ergotamine and rizatriptan were given together, the increase in toe-arm systolic blood pressure gradient was similar to that when ergotamine was given alone.

No change in the ECG parameters measured was observed when two 10-mg doses of Rizatriptan Benzoate Tablets, separated by 2 hours, were studied in 157 migraine patients (age range 18 to 72 years) during a migraine attack.

TOXICOLOGY

Acute Toxicity

The approximate oral LD₅₀ of rizatriptan was 700 mg/kg and 2227 mg/kg in mice and rats, respectively. The approximate intravenous LD₅₀ values were 89 and 141 mg/kg in mice and rats, respectively.

Chronic Toxicity

The toxicity potential of rizatriptan was evaluated in a series of repeat dose oral toxicity studies up to one year in dogs and rats and up to 14 weeks in mice. There were no adverse findings that would preclude administration of rizatriptan benzoate at the recommended therapeutic dosages to humans.

Carcinogenesis

The carcinogenic potential of rizatriptan was evaluated in a 106-week study in rats and a 100-week study in mice at oral doses of up to 125 mg/kg/day (625-fold the human dose of 10 mg or 0.2 mg/kg). These doses produced exposure margins (AUC ratios) of up to 600- and 400-fold in rats and mice, respectively, over the human systemic exposure at a therapeutic dose of 10 mg (0.2 mg/kg). For both rats and mice, no evidence of carcinogenicity was seen with increasing doses of rizatriptan.

Mutagenesis

Rizatriptan, with and without metabolic activation, was neither genotoxic, mutagenic, nor clastogenic in all *in vitro* and *in vivo* genetic toxicity studies, including: microbial mutagenesis, *in vitro* chromosome aberration assays, *in vitro* V-79 mammalian cell mutagenesis assays, an *in vitro* alkaline elution/rat hepatocyte assay, and an *in vivo* chromosome aberration assay in mouse bone marrow.

Reproduction

No adverse effects on fertility or reproductive performance, and no fetal toxicity or malformations were observed in female and male rats (except slightly decreased body weight at the high dose) given oral doses of rizatriptan up to 100 and 250 mg/kg/day, respectively (500- and 1250-fold the human dose of 10 mg or 0.2 mg/kg). In addition, no adverse effects on reproductive parameters were detected during early or late gestation, or during the lactation period. These doses provided exposure margins more than 900-fold over the human systemic exposure, based on the AUC ratio derived from rat maternal drug levels compared to humans treated with 10 mg (0.2 mg/kg). High placental transfer occurred, as evidenced by rat fetal plasma levels of 20 to 40% of the maternal plasma levels. High milk transfer occurred, and resulted in rat milk levels that were 5-fold, or greater, the maternal plasma levels. Although high maternal, fetal and neonatal exposure to rizatriptan occurred in these studies, no adverse treatment-related effects were observed on F₁ survival, development, behavior, reproductive performance, or testicular histology, nor were there any effects seen in the F₂ offspring.

No adverse effects on development, and no fetal toxicity or malformations were observed in pregnant rabbits (except slightly decreased body weight at the high dose) given oral doses of rizatriptan up to 50 mg/kg/day (250-fold the human dose of 10 mg or 0.2 mg/kg). These doses produced high maternal drug levels, resulting in a 475-fold exposure margin, based on the AUC ratio derived from rabbit maternal drug levels compared to humans treated with 10 mg (0.2 mg/kg). High placental transfer occurred with rabbit fetal tissue levels reaching 42 to 49% of the maternal plasma levels.

Development

There were no adverse effects on fetal development in rats or rabbits exposed to large multiples of the human therapeutic dose of rizatriptan during early and late gestation. High placental transfer of rizatriptan was documented by fetal plasma and tissue levels.

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5. MAXALT® Product Monograph, Merck Frosst Canada Ltd., Revision Date: October 4, 2011, Control Number: 148699.
6. A comparative bioavailability study was performed on TEVA-RIZATRIPTAN 10 mg tablets and MAXALT® 10 mg tablets, under fasting conditions. Data on file at Teva Canada Limited.

PART III: CONSUMER INFORMATION

**TEVA-RIZATRIPTAN
rizatriptan benzoate tablets**

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

Please read this leaflet carefully before you take TEVA-RIZATRIPTAN. It provides a summary of the information available on your medication. Please do not throw it away. Keep it for reference until you have finished your medicine. This leaflet does not contain all the information available on TEVA-RIZATRIPTAN. For further information or advice, ask your physician or pharmacist.

ABOUT THIS MEDICATION

The name of your medicine is TEVA-RIZATRIPTAN. It can only be obtained by prescription from your physician. The decision to use TEVA-RIZATRIPTAN is one that you and your physician 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 postmenopausal female, or a male over 40), tell your physician. Your physician should evaluate you for heart disease in order to determine whether TEVA-RIZATRIPTAN is appropriate for you.

What the medication is used for

TEVA-RIZATRIPTAN is intended to relieve your migraine headache and other associated symptoms of a migraine attack. **TEVA-RIZATRIPTAN should not be used continuously to prevent or reduce the number of attacks you experience. Use TEVA-RIZATRIPTAN 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. TEVA-RIZATRIPTAN narrows the vessels and relieves the pain and other symptoms of migraine headache.

When it should not be used

Do not take TEVA-RIZATRIPTAN if you:

- are allergic to any of the ingredients (see **What the nonmedicinal ingredients are** section)
- have uncontrolled or severe high blood pressure
- have heart disease or history of heart disease
- have severe liver disease
- take monoamine oxidase (MAO) inhibitors such as moclobemide, phenelzine, tranylcypromine, or pargyline, or have taken MAO inhibitors within the last two weeks.

TEVA-RIZATRIPTAN should not be used to relieve pain other than that associated with migraine headache.

TEVA-RIZATRIPTAN should not be used within 24 hours of treatment with another 5-HT₁ agonist such as sumatriptan

(Imitrex), naratriptan (Amerge) or zolmitriptan (Zomig), or ergotamine-type medications such as ergotamine, dihydroergotamine or methysergide.

Please also see WARNINGS AND PRECAUTIONS.

What the medicinal ingredient is:

rizatriptan benzoate

What the important nonmedicinal ingredients are:

Lactose monohydrate, sodium starch glycolate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

TEVA-RIZATRIPTAN (rizatriptan benzoate) is available as a 5 mg or 10 mg white to off-white tablet containing either 5 mg or 10 mg of rizatriptan.

WARNINGS AND PRECAUTIONS

If the answer to any of the following questions is YES or if you do not know the answer, then please speak with your physician before you take any TEVA-RIZATRIPTAN.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breast feeding?
- **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, rapid heartbeats or irregular heartbeats? Do you have angina?**
- Have you ever had heart or blood vessel disease? 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? Are you post-menopausal, or a male over 40?**
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine 5-HT₁ agonist medications such as Imitrex (sumatriptan succinate/sumatriptan) or Amerge (naratriptan as naratriptan hydrochloride), Zomig (zolmitriptan) or migraine medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medications for depression such as selective serotonin reuptake inhibitors (SSRIs) such as sertraline, escitalopram oxalate, and fluoxetine or serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, duloxetine, or monoamine oxidase inhibitors (MOIs)?
- Have you ever experienced numbness on one side of your body when you have a headache?
- Have you ever had, or do you have epilepsy or seizures?
- Have you ever had, or do you have liver disease or kidney disease?
- Is this headache different from your usual migraine attacks?
- Are you over 65 years of age?

If you are not sure whether you should take TEVA-RIZATRIPTAN, contact your physician or pharmacist.

TEVA-RIZATRIPTAN use during pregnancy:

Do not use TEVA-RIZATRIPTAN 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 physician.

INTERACTIONS WITH THIS MEDICATION

If you are taking any other migraine medication, check with your physician first before taking TEVA-RIZATRIPTAN and inform your physician of any other medications you may be taking, including those obtained without a prescription.

Do not take TEVA-RIZATRIPTAN or if you take monoamine oxidase (MAO) inhibitors such as moclobemide, phenelzine, tranylcypromine, or pargyline, or have taken MAO inhibitors within the last two weeks.

Ask your physician for instructions about taking TEVA-RIZATRIPTAN or if you are taking selective serotonin reuptake inhibitors (SSRIs) such as sertraline, escitalopram oxalate, and fluoxetine or serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, duloxetine for depression. A life-threatening condition called serotonin syndrome can happen when medicines called triptans, such as TEVA-RIZATRIPTAN, and medicines used to treat depression and mood disorders called SSRIs and SNRIs are used together. Signs and symptoms of serotonin syndrome include the following: restlessness, diarrhea, hallucinations, coma, loss of coordination, nausea, fast heart beat, vomiting, increased body temperature, changes in blood pressure and overactive reflexes.

PROPER USE OF THIS MEDICATION

REMEMBER: this medicine was prescribed only for YOU. Only a physician 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.

Usual dose

For adults, the usual dosage is 5 or 10 mg, as recommended by your physician. The dose should be taken as soon as your migraine appears, but it may be taken at any time during your migraine headache.

If you are taking a tablet, swallow your dose with water.

A second dose may be taken if your headache returns. Repeat doses cannot be taken any sooner than 2 hours following the first dose. Do not take more than 20 mg in any 24-hour period.

For any attack where you have no response to the first dose, do not take a second dose without first consulting your physician.

Overdose:

In the case of 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 rizatriptan benzoate users have not experienced any significant problems, you should be aware of the following side effects:

Common side effects

- **sensations of pain, pressure or tightness in the chest, neck, throat, jaw or arms. If this happens to you, then discuss it with your physician before using any more TEVA-RIZATRIPTAN. If the chest pain is severe (may resemble an angina attack) or does not go away, stop taking drug and call your physician immediately.**
- tingling, heat, heaviness or pressure, dizziness, tiredness, or feeling sick. Tell your physician if you have any of these symptoms.
- drowsiness. Do not drive or operate machinery until you are sure that you are not drowsy.
- irregular or rapid heartbeats. If this happens to you, stop taking drug and then discuss it with your physician before using any more TEVA-RIZATRIPTAN.

Uncommon side effects

- Rapid onset of numbness or weakness on one side of the body (often beginning in one arm). If this occurs, stop taking drug and call your physician immediately.
- Muscle pain. If this occurs, stop taking drug and call your physician immediately.

Rare side effects

- shortness of breath, wheeziness, heart throbbing, swelling of the eyelids, face, tongue or lips; or a skin rash or skin lumps or hives or spasms of blood vessels of the extremities including coldness and numbness of the hands and feet. These effects happen rarely, but if any do occur, do not take any more TEVA-RIZATRIPTAN and contact your physician immediately.
- sudden or severe abdominal pain. If this occurs, stop taking drug and call your physician immediately.

Very rare side effects

- There have been very rare reports of seizures. If this occurs, stop taking drug and call your physician immediately.
- Spasm of the blood vessels of the colon (large bowel). If this occurs, stop taking drug and call your physician immediately.

If you feel unwell in any other way or have symptoms that you do not understand or find distressing, you should contact your physician immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Common	sensations of pain, pressure or tightness in the chest, neck, throat, jaw or arms			√
	tingling, heat, heaviness or pressure in any part of the body	√		
	headache, dizziness, tiredness, nausea, vomiting, dry mouth, drowsiness	√		
	Irregular or rapid heartbeats			√
Uncommon	Rapid onset of numbness or weakness on one side of the body (often beginning in one arm)			√
	muscle pain			√
Rare	shortness of breath, wheeziness, heart throbbing, swelling of the eyelids, face, tongue or lips; or a skin rash or skin lumps or hives or spasms of blood vessels of the extremities			√
	sudden or severe abdominal pain			√
Very rare	seizures			√
	spasm of the blood vessels of the colon (large bowel)			√

This is not a complete list of side effects. For any unexpected effects while taking TEVA-RIZATRIPTAN, contact your physician or pharmacist.

HOW TO STORE IT

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

If your physician decides to stop your treatment, do not keep any leftover medicine unless your physician tells you to do so.

If your medicine has expired, do not use it. It is recommended to take leftover medication to a pharmacy for proper 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
Postal Locator 0701D
Ottawa, ON K1A 0K9

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 the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:
1-800-268-4127 ext. 5005 (English);
1-877-777-9117 (French)
or druginfo@tevacanada.com

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