PRODUCT MONOGRAPH

Pr ALMOTRIPTAN

Almotriptan (as almotriptan malate) Tablets

12.5 mg

5-HT_1 Receptor Agonist
Migraine Therapy

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Date of Revision:
August 9, 2017

Submission Control No.: 208235

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet 12.5 mg	Hypromellose, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, sodium stearyl fumarate, and titanium oxide**.**

INDICATIONS AND CLINICAL USE

Adults (> 18 years of age)
Almotriptan (almotriptan malate) tablets are indicated for the acute treatment of migraine attacks with or without aura.

Almotriptan 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 Almotriptan have not been established for cluster headache which is present in an older, predominantly male population.

Almotriptan should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Almotriptan, the diagnosis of migraine should be reconsidered before Almotriptan is administered to treat any subsequent attacks.

Pediatrics
Adolescents (12-17 years of age)
Almotriptan is indicated for the acute treatment of migraine headache pain in patients 12-17 years of age who have a history of migraine attacks with or without aura usually lasting 4 hours or longer (when untreated). Efficacy of Almotriptan on migraine-associated symptoms of nausea, photophobia and phonophobia has not been established.

Children (< 12 years of age)
Almotriptan is not indicated for use in patients under 12 years of age.

Geriatrics (> 65 years of age)
Clinical studies of almotriptan did not include sufficient numbers of subjects over 65 years of age to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal, cardiac, and hepatic function, and of concomitant disease or other drug therapy (See WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

Almotriptan (almotriptan malate) is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- 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 Almotriptan. 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).
- patients with uncontrolled hypertension because almotriptan may increase blood pressure (see WARNINGS AND PRECAUTIONS).
- within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication, such as dihydroergotamine or methysergide.
- patients with hemiplegic, ophthalmoplegic or basilar migraine.
- patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION)

WARNINGS AND PRECAUTIONS

General
Almotriptan should only be used where a clear diagnosis of migraine has been established. Almotriptan should be administered with caution to patients with diseases that may alter the absorption, metabolism or excretion of drugs, such as those with mild to moderate hepatic impairment or with impaired renal function (see ACTION AND CLINICAL

PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION). Treatment is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

Medication Overuse Headache: Overuse of acute migraine treatments has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Hypersensitivity to Sulfonamides

Caution should be exercised when prescribing almotriptan to patients with known hypersensitivity to sulfonamides. The chemical structure of almotriptan contains a sulfonyl group, which is structurally different from a sulfonamide. Cross-sensitivity to almotriptan in patients allergic to sulfonamides has not been evaluated.

Ability to Operate Machinery and Vehicles

Almotriptan may cause dizziness, somnolence, visual disturbances, and other CNS symptoms that can interfere with driving or operating machinery. Patients should be advised to avoid driving a car, operating complex machinery, or engage in hazardous activities until they are reasonably certain that almotriptan does not affect them adversely.

Carcinogenesis and Mutagenesis

The carcinogenic potential of almotriptan was evaluated by oral gavage for up to 103 weeks in mice at doses of up to 250 mg/kg/day, and in rats for up to 104 weeks at doses up to 75 mg/kg/day. These doses were associated with plasma exposures (AUC) to parent drug that were approximately 40 and 78 times, in mice and rats respectively, the plasma AUC observed in humans receiving the MRDD of 25 mg. Because of high mortality rates in both studies, which reached statistical significance in high-dose female mice, all female rats, all male mice and high-dose female mice were terminated between weeks 96 and 98. There was no increase in tumors related to almotriptan administration.

Almotriptan was not mutagenic, with or without metabolic activation, when tested in two gene mutation assays, the Ames test and the *in vitro* thymidine locus mouse lymphoma assay. Almotriptan was not determined to be clastogenic in two *in vitro* cytogenetics assays in human lymphocytes and an *in vivo* mouse micronucleus assay. Almotriptan produced an equivocal weakly positive response in *in vitro* cytogenetics assays in human lymphocytes.

Cardiovascular

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

Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, almotriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT_1 agonists (including almotriptan) not be given to patients in whom unrecognized coronary artery

disease (CAD) is predicted by the presence of risk factors such as: 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 examination 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 diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiogram (ECG) or other evaluations reveal findings indicative of, or consistent with, coronary artery vasospasm, or myocardial ischemia, almotriptan should not be administered (see CONTRAINDICATIONS).

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

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of almotriptan take place in a clinical setting, such as the physician's office or a similarly staffed medical facility, unless the patient has previously received almotriptan. Because cardiac ischemia can occur in the absence of any clinical symptoms, consideration should be given to obtaining an ECG during the interval immediately following the first use of almotriptan in a patient 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.

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

It is recommended that patients who are intermittent long-term users of almotriptan and who have or acquire risk factors predictive of CAD as described above undergo periodic interval cardiovascular evaluation as they continue to use almotriptan.

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

As with other 5-HT_1 agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck and jaw have been reported after treatment with almotriptan. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. Because drugs in this class, including almotriptan 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 the medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist, are candidates for further evaluation (see

CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists
Serious adverse cardiac events, including acute myocardial infarction have been reported within a few hours following administration of almotriptan. Life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Due to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described below should be considered for all agents of this class.

Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Almotriptan can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease.

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

Premarketing experience with almotriptan
Among the 3865 subjects/patients who received almotriptan in premarketing clinical trials, one patient was hospitalized for observation after a scheduled ECG was found to be abnormal (negative T-waves on the left leads) 48 hours after taking a single 6.25 mg dose of almotriptan. The patient, a 48-year-old female, had previously taken 3 other doses for earlier migraine attacks. Myocardial enzymes at the time of the abnormal ECG were normal. The patient was diagnosed as having had myocardial ischemia and it was also found that she had a family history of coronary disease. An ECG performed 2 days later was normal, as was a follow-up coronary angiography. The patient recovered without incident.

Postmarketing experience with almotriptan
Serious cardiovascular events have been reported in association with the use of almotriptan in both adults and adolescents. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to definitely determine the proportion of the reported cases that were actually caused by almotriptan or to reliably assess causation in individual cases (see Post-Market Adverse Drug Reactions).

Cerebrovascular Events and Fatalities with 5-HT_1 Agonists
Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with other 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 belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with almotriptan, 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, however, that patients who suffer from migraine may have an increased risk of certain cerebrovascular events such as stroke, hemorrhage or transient ischemic attack.

Other Vasospasm-Related Events
5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increases in Blood Pressure
Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. Almotriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, almotriptan 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 volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mmHg, respectively). The effect of almotriptan on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mmHg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant (see ADVERSE REACTIONS and WARNINGS AND PRECAUTIONS).

Special Cardiovascular Pharmacology Studies with another 5-HT_1 Agonist
In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT_1 agonist is not known.

Similar studies have not been done with almotriptan. 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.

Dependence/Tolerance

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

Endocrine and Metabolism

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 almotriptan and SSRIs (e.g., fluoxetine, paroxetine, sertraline) or SNRIs (e.g., venlafaxine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see WARNINGS AND PRECAUTIONS, Drug Interactions).

Hepatic/Biliary/Pancreatic

Almotriptan should be used with caution in patients with mild to moderate hepatic impairment and treatment is contraindicated in patients with severe hepatic disease. (see CONTRAINDICATIONS). The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg is recommended (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

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 almotriptan.

Ophthalmologic

Corneal Opacities

Three male dogs (out of a total of 14 treated) in a 52-week toxicity study of oral almotriptan developed slight corneal opacities that were noted after 51, but not after 25, weeks of treatment. The doses at which this occurred were 2, 5, and 12.5 mg/kg/day. The opacity reversed in the affected dog at 12.5 mg/kg/day after a 4-week drug-free period. Systemic exposure (plasma AUC) to parent drug at 2 mg/kg/day was approximately 2.5 times the exposure in humans receiving the maximum recommended daily dose of 25 mg. A no-effect dose was not established.

Renal

Almotriptan should be used with caution in patients with severe renal impairment. The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Sensitivity/Resistance

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred in patients receiving other 5-HT_1 agonists. 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, almotriptan should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists (see ADVERSE REACTIONS and WARNINGS AND PRECAUTIONS).

Sexual Function/Reproduction

When female rats received almotriptan by oral gavage prior to and during mating and up to implantation at doses of 25, 100, and 400 mg/kg/day, prolongation of the estrous cycle was observed at a dose of 100 mg/kg/day (exposure, based on mg/m^2, was approximately 40 times exposure in humans receiving the maximum recommended daily dose (MRDD) of 25 mg). No effects on fertility were noted in female rats at 25 mg/kg/day (exposure approximately 10 times human exposure at MRDD). No adverse effects were noted in male rats at 400 mg/kg/day (160 times the human exposure based on mg/m^2).

Skin

Binding to Melanin-Containing Tissues

When pigmented rats were given a single oral dose of 5 mg/kg of radiolabelled almotriptan, the elimination half-life of radioactivity from the eye was 22 days, suggesting that almotriptan and/or its metabolites may bind to the melanin of the eye. Because almotriptan could accumulate in the melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues over extended use. However, no adverse ocular effects related to treatment with almotriptan were noted in any of the toxicity studies. Although no systemic monitoring of ophthalmic function was undertaken in clinical trials, and no specific recommendations for ophthalmic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmic effects.

Special Populations

Pregnant Women: When almotriptan was administered orally during organogenesis to pregnant rats at doses of 125, 250, 500 and 1000 mg/kg/day, an increase in embryolethality was seen at the 1000 mg/kg/day dose (maternal exposure [based on plasma AUC of parent drug] was approximately 958 times the human exposure at MRDD of 25 mg). Increased incidences of fetal skeletal variations (decreased ossification) were noted at doses greater than the no-observed-effect level in rats of 125 mg/kg/day (maternal exposure 80 times human exposure at MRDD). Similar studies in rabbits conducted with almotriptan at doses of 5, 20 and 60 mg/kg/day demonstrated increases in embryolethality at 60 mg/kg/day (maternal exposure, based on mg/m^2,

50 times human exposure at MRDD). When almotriptan was administered to rats throughout the periods of gestation and lactation at doses of 25, 100 and 400 mg/kg/day, gestation length was increased and litter size and offspring body weight were decreased at the high dose (maternal exposure, based on mg/m^2, 160 times human exposure at MRDD). The decrease in pup weight persisted throughout lactation. The no-observed-effect level in this study was 100 mg/kg/day (maternal exposure 40 times human exposure at MRDD).

There have been no adequate and well-controlled studies or clinical trials in pregnant women; therefore almotriptan should only be used during pregnancy if the potential benefit justifies the risk to the fetus.

Nursing Women: It is not known whether almotriptan is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when almotriptan is administered to a nursing woman. Levels of almotriptan in rat milk were up to 7 times higher than in rat plasma. Infant exposure may be minimized by avoiding breast feeding for 24 hours after treatment.

Paediatrics
Adolescents (12-17 years of age)
The pharmacokinetics of almotriptan have been evaluated in adolescent patients aged 12-17 years. The pharmacokinetic parameters in adolescents were similar to those of adults with the exception of oral clearance which was slightly higher (see CLINICAL TRIALS).

Children (< 12 years of age)
Safety and efficacy of almotriptan in pediatric patients under the age of 12 years have not been studied and almotriptan is not indicated for use in this patient population.

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 (See Post-Market Adverse Drug Reactions).

Geriatrics (> 65 years of age)
Clinical studies of almotriptan did not include sufficient numbers of subjects over 65 years of age to determine whether they respond differently from younger subjects. Renal and total clearance, and amount of drug excreted in the urine were lower in elderly non-migraineur volunteers (age 65 to 76 years) than in younger non-migraineur volunteers (age 19 to 34 years), resulting in longer terminal half-life and higher area under the plasma concentration-time curve. Although clearance of almotriptan was lower in elderly volunteers, there were no differences in the safety and tolerability between the two populations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal, cardiac, and hepatic function, and of concomitant disease or other drug therapy (See INDICATIONS and WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Serious cardiac events, including some that have been fatal, have occurred following use of other 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasms, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Serious cardiac events, including myocardial infarction, coronary artery vasospasm and intermediate coronary syndrome, have occurred following the use of almotriptan tablets. These events are extremely rare and have been reported mostly in patients with cardiovascular risk factors (see WARNINGS AND PRECAUTIONS and Post-Market Adverse Drug Reactions).

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.

As with other 5-HT_1 agonists, almotriptan 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 limbs.

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. Almotriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mmHg, respectively). The effect of almotriptan on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mmHg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant (see also CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Adverse events were assessed in controlled clinical trials that included 1840 patients who received one or two doses of almotriptan and 386 patients who received placebo.

The most common adverse events during treatment with almotriptan were nausea, somnolence, headache, paresthesia, and dry mouth. In long-term, open-label studies where patients were allowed to treat multiple attacks for up to one year, 5% (63 out of 1347 patients) withdrew due to adverse experiences.

Tables 1 and 2 list the adverse events in clinical trials of adult patients and adolescents (12-17 years of age), respectively, that occurred in at least 1% of the patients treated with almotriptan, and at an incidence greater than in patients treated with placebo, regardless of drug relationship. These events 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 behaviour, and the kinds of patients treated may differ.

Table 1 Incidence of Adverse Events in Controlled Clinical Trials in adults (Reported in at Least 1% of Patients Treated with Almotriptan malate tablets and at an Incidence Greater than Placebo)

	Percentage of Patients Reporting the Event		
Adverse Event	**Placebo (n= 386) (%)**	**Almotriptan 6.25 mg (n= 527) (%)**	**Almotriptan 12.5 mg (n= 1313) (%)**
Digestive			
Nausea	1	1	2
Dry Mouth	0.5	1	1
Nervous			
Paresthesia	0.5	1	1

Table2 Adverse Drug Reactions Reported by ≥1% of Adolescent Patients Treated with Almotriptan malate tablets in 1 Placebo-Controlled, Double-Blind Clinical Trial

System/Organ Class Adverse Reaction	**Placebo (n=172) (%)**	**Almotriptan 6.25 mg (n=180) (%)**	**Almotriptan 12.5 mg (n=182) (%)**	**Almotriptan 25 mg (n=186) (%)**
Nervous system disorders				
Dizziness	2	4	3	6
Somnolence	2	<1	5	3
Headache	2	1	2	1
Paresthesia	<1	<1	1	1
Gastrointestinal disorders				
Nausea	0	1	3	2
Vomiting	<1	2	0	2

Almotriptan is generally well tolerated. Most adverse events were mild in intensity and were transient, and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, age, presence of aura, or use of prophylactic medications or oral contraceptives. There were insufficient data to assess the effect of race on the incidence of adverse events.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The frequencies of less commonly reported adverse events are presented below. However, the role of almotriptan 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 almotriptan in controlled clinical trials and reported an event, divided by the total number of patients exposed to almotriptan in these studies. All reported events are included, except the ones already listed in the previous table, and those unlikely to be drug related. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Adults

Total Body System: *Frequent* was headache. *Infrequent* were abdominal cramp or pain, asthenia, chills, back pain, chest pain, neck pain, fatigue, and rigid neck. *Rare* were fever and photosensitivity reaction.

Cardiovascular: *Infrequent* were vasodilation, palpitations, and tachycardia. *Rare* were intermediate coronary syndrome, abnormal cardiac rhythm, hypertension, and syncope.

Digestive: *Infrequent* were diarrhea, vomiting, and dyspepsia. *Rare* were decreased appetite, increased appetite, colitis, gastritis, gastroenteritis, esophageal reflux, increased thirst, and increased salivation.

Metabolic: *Infrequent* were hyperglycemia and increased serum creatine phosphokinase. *Rare* were increased gamma glutamyl transpeptidase and hypercholesteremia.

Musculoskeletal: *Infrequent* were myalgia and muscular weakness. *Rare* were arthralgia, arthritis, and myopathy.

Nervous: *Frequent* were dizziness and somnolence. *Infrequent* were tremor, vertigo, anxiety, hypesthesia, restlessness, CNS stimulation, insomnia, and shakiness. *Rare* were change in dreams, impaired concentration, abnormal coordination, depressive symptoms, euphoria, hyperreflexia, hypertonia, nervousness, neuropathy, nightmares, and nystagmus.

Respiratory: *Infrequent* were pharyngitis, rhinitis, dyspnea, laryngismus, sinusitis, bronchitis, and epistaxis. *Rare* were hyperventilation, laryngitis, and sneezing.

Skin：*Infrequent* were diaphoresis, dermatitis, erythema, pruritus, and rash.

Special Senses：*Infrequent* were ear pain, conjunctivitis, eye irritation, hyperacusis, and taste alteration. *Rare* were diplopia, dry eyes, eye pain, otitis media, parosmia, scotoma, and tinnitus.

Urogenital：Dysmenorrhea was *infrequent*.

Paediatrics

Adolescents (12-17 years of age)

Total Body System: *Infrequent* were asthenia, chest discomfort, chest pain, discomfort, fatigue, feeling hot, gastroenteritis, increased body temperature, lethargy, photosensitivity reaction, thirst, urinary tract infections, vasoconstriction and viral infection.

Blood and Lymphatic System: *Infrequent* were anaemia, eosinophilia, lymphocytosis and neutropenia.

Cardiovascular: *Infrequent* were electrocardiogram QT prolonged, nodal rhythm, palpitations, sinus arrhythmia, supraventricular extrasystoles and tachycardia.

Digestive: *Infrequent* were abdominal pain, diarrhea, dry mouth, oral hypoaesthesia and upper abdominal pain.

Metabolism: *Infrequent* were anorexia, diabetes mellitus insulin-dependent, increased blood creatine phosphokinase and increased monocyte count.

Musculoskeletal: *Infrequent* were muscle cramp, limb injury, muscle stiffness, muscle tightness, musculoskeletal stiffness, myalgia, neck pain, pain in extremity and wrist fracture.

Nervous: *Infrequent* were hyperaesthesia, hypoaesthesia, migraine, psychomotor hyperactivity, tremor, trismus and vertigo.

Respiratory: *Infrequent* were cough, dry throat, dyspnoea, influenza, nasal congestion, nasopharyngitis, pharyngolaryngeal pain, rhinitis, sinusitis, throat irritation, throat tightness, upper respiratory infections and wheezing.

Skin: *Infrequent* were flushing, generalized pruritus, increased sweating, pallor, pruritus, rash, skin laceration and warm skin.

Special Senses: *Infrequent* were conjunctivitis, blurred vision, ear pain and otitis media.

Urogenital: Dysmenorrhea was *infrequent.*

Long-term Safety

Adults (> 18 years of age)

In a long-term open label study, 762 adult patients treated 13,751 migraine attacks with almotriptan over a period of up to 1 year. Migraine headaches could be treated with either a single dose of 12.5 mg almotriptan or an initial 12.5 mg dose followed by a second 12.5 mg dose if needed. In this study, 3% (24 of 762) of patients withdrew due to an adverse experience. The most common adverse events (defined as occurring in more than 3% of patients) in descending order frequency were as follows: back pain (8%), bronchitis (6.4%), influenza-like symptoms

(5.8%), pharyngitis (4.6%), vomiting (4.2%), rhinitis (4.1%), skeletal pain (3.4%) and sinusitis (3.4%). Due to the lack of placebo control in this study, the role of almotriptan in causation cannot be reliably determined.

Pediatrics

Adolescents (12-17 years of age)

In a long-term open label safety study in adolescents, 420 patients with a history of migraine with or without aura treated each migraine attack with one or two doses of almotriptan (12.5 mg each) for up to 12 months. A total 319 patients (71.4%) completed the study. Ten (2.4%) of the subjects withdrew from the study due to one or more adverse events. Adverse events that occurred in ≥2% of subjects in decreasing order of subject frequency were: nasopharyngitis (12.4%), sinusitis (6.9%), upper respiratory tract infection (6.7%), pharyngolaryngeal pain (6.4%), nausea (6.0%), vomiting (5.5%), streptococcal pharyngitis (4.3%), nasal congestion (4.0%), cough (3.8%), pyrexia (3.6%), viral gastroenteritis (3.6%), influenza (3.3%), viral infection (3.1%), joint sprain (2.9%), pharyngitis (2.6%), upper abdominal pain (2.4%), and bronchitis (2.1%). Some of the adverse events that occurred in between 1% and 2% of subjects were: dizziness (1.9%), diarrhea (1.9%), insomnia (1.9%), dysmenorrhea (1.7%) and syncope (1.4%).

Post-Market Adverse Drug Reactions

In addition to the adverse experiences reported during clinical trials of almotriptan the following adverse events have been reported in patients receiving marketed almotriptan from worldwide use since approval. Due to the uncontrolled nature of post-marketing surveillance, it is not possible to definitely determine the proportion of the reported cases that were actually caused by almotriptan or to reliably assess causation. The adverse drug reactions are ranked by frequency, using the following convention:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
Very rare < 1/10,000

Serious cardiovascular adverse events, including acute myocardial infarction, coronary vasospasm and angina pectoris have been reported within a few hours following administration of almotriptan.

Although very rare, almotriptan can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and PRECAUTIONS).

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 (See WARNINGS AND PRECAUTIONS, Special Populations).

Adults

Adverse Event	Reporting Case			
	Common	Uncommon	Rare	Very Rare
Blood and Lymphatic System Disorders				
• agranulocytosis				√
• spontaneous haematoma				√
Cardiac Disorders				
• Coronary vasospasm				√
• Myocardial infarction				√
Eye Disorders				
• blepharospasm				√
• blindness				√
• conjunctival haemorrhage				√
• lacrimal disorder				√
• mydriasis				√
• photopsia				√
• visual impairment (not known)				
• vision blurred (not known)				
Gastrointestinal Disorders				
• aphthous stomatitis				√
• cheilitis				√
• dysphagia				√
• lip pain				√
• lip swelling				√
• swollen tongue				√
• intestinal ischemia (not known)				
General Disorders and Administration Site Conditions				
• face oedema				√
• facial pain				√
• feeling abnormal				√
• hypothermia				√
• malaise				√
• oedema peripheral				√
• sensation of foreign body				√
• sense of oppression				√
• therapeutic response decreased				√
Immune System Disorders				
• anaphylactic shock				√
• anaphylactoid reaction				√
Injury, Poisoning and Procedural Complications				
• accidental poisoning				√
• toxicity to various agents				√
Investigations				
• blood pressure decreased				√
Musculoskeletal and Connective Tissue Disorders				
• muscle spasms				√
• muscle tightness				√
• musculoskeletal stiffness				√
• pain in extremity				√
• pain in jaw				√
• sensation of heaviness				√
• bone pain		√		

Adverse Event	Reporting Case			
	Common	Uncommon	Rare	Very Rare
Nervous System Disorders				
• aphasia				√
• brain stem infarction				√
• burning sensation				√
• cerebral ischaemia				√
• convulsion				√
• depressed level of consciousness				√
• dysarthria				√
• dysgeusia				√
• hemiplegia				√
• loss of consciousness				√
• memory impairment				√
• partial seizures with secondary generalisation				√
• serotonin syndrome				√
• speech disorder				√
Psychiatric Disorders				
• confusional state				√
• disorientation				√
• hallucination				√
• hallucination, auditory				√
• panic disorder				√
• sopor				√
• suicide ideation				√
• withdrawal syndrome				√
Renal and Urinary Disorders				
• micturition urgency				√
• polyuria				√
Reproductive System and Breast Disorders				
• breast pain				√
• menorrhagia				√
• metrorrhagia				√
• vaginal haemorrhage				√
Respiratory, Thoracic and Mediastinal Disorders				
• respiratory distress				√
• respiratory failure				√
• respiratory fatigue				√
Skin and Subcutaneous Tissue Disorders				
• angioedema				√
• cold sweat				√
• hyperhidrosis				√
• swelling face				√
• urticaria				√
Vascular Disorders				
• flushing				√
• pallor				√
• peripheral coldness				√
• vascular insufficiency				√

Paediatrics
Adolescents (12-17 years of age)

Adverse Event	Reporting Case			
	Common	Uncommon	Rare	Very Rare
Cardiac Disorders				
• bundle branch block				√
• sinus tachycardia				√
Ear and Labyrinth Disorders				
• vertigo				√
Gastrointestinal Disorders				
• nausea				√
General Disorders and Administration Site Conditions				
• chest pain				√
• fatigue				√
Musculoskeletal and Connective Tissue Disorders				
• musculoskeletal stiffness				√
Nervous System Disorders				
• burning sensation				√
• loss of consciousness				√
• pyramidal tract syndrome				√
• somnolence				√
Reproductive System and Breast Disorders				
• breast tenderness				√

DRUG INTERACTIONS

Overview
All drug interaction studies were performed in healthy volunteers using a single 12.5 mg dose of almotriptan and multiple doses of the other drug. Interaction studies were performed with monamine oxidase A inhibitors, beta-blockers, selective serotonin re-uptake inhibitors, calcium channel blockers or inhibitors of Cytochrome P450 isoenzymes 3A4 and 2D6. There are no *in vivo* interaction studies assessing the effect of almotriptan on other drugs.

Drug-Drug Interactions

Table3 Established or Potential Drug-Drug Interactions

<Proper name>	Ref	Effect	Clinical comment
Ergot-containing Drugs	T	additive	These drugs have been reported to cause prolonged vasospastic reactions. As there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (dihydroergotamine or methylsergide) and almotriptan malate within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

<Proper name>	Ref	Effect	Clinical comment
Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors	C	Life-threatening serotonin syndrome	Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see WARNINGS AND PRECAUTIONS). Coadministration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP2D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased by 18%. This difference is not clinically significant.
Monoamine oxidase inhibitors (MAOIs)	CT/T	Decrease in almotriptan clearance and an increase in C_{max}. No dose adjustment necessary Serotoninergic syndrome with MAOIs cannot be ruled out.	Coadministration of almotriptan and moclobemide (150 mg BID for 8 days) resulted in a 27% decrease in almotriptan clearance and an increase in C_{max} of approximately 6%. No dose adjustment is necessary.
Propranolol	CT	No significant changes	Coadministration of almotriptan and propranolol (80 mg BID for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.
Verapamil	CT	Not clinically significant	Coadministration of almotriptan and verapamil (120 mg sustained-release tablets BID for 7 days), an inhibitor of CYP4503A4, resulted in a 20% increase in the area under the plasma concentration-time curve, and in a 24% increase in maximal plasma concentrations of almotriptan. Neither of these changes is clinically significant.
Other 5-$HT_{1B/1D}$ agonists	CT	Contraindicated	Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of treatment with almotriptan is contraindicated (see CONTRAINDICATIONS).

<Proper name>	Ref	Effect	Clinical comment
Ketoconazole and other potent CYP3A4 inhibitors	CT/T	Additive	Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg QD for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (e.g. itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.
Herbal preparations containing St. John's Wort (*Hypericum perforatum*)	T	Undesirable effects may be more common during concomitant use with triptans.	

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

Drug-Laboratory Interactions

Almotriptan is not known to interfere with any commonly employed clinical laboratory tests. No specific laboratory tests are recommended for monitoring patients.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Almotriptan is not indicated for use in paediatric patients under 12 years of age (see INDICATIONS).

Hepatic Impairment

Treatment is contraindicated in patients with severe hepatic disease (see CONTRAINDICATIONS). There are no data including no pharmacokinetics of almotriptan that have been assessed in this population. The maximum decrease expected in the clearance of almotriptan due to hepatic impairment is 60%. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and WARNINGS AND PRECAUTIONS).

Renal Impairment

In patients with severe renal impairment, the clearance of almotriptan was decreased. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

Adults and Adolescents (≥12 years of age)

In controlled clinical trials, single doses of 6.25* mg and 12.5 mg of almotriptan were effective for the acute treatment of migraine in adults and adolescents of age 12 to 17 years. In some adult patients, the 12.5 mg dose tends to be a more effective dose (see CLINICAL TRIALS). However, the 12.5 mg dose was generally associated with a higher frequency of adverse events in adolescents. Individuals may vary in response to doses of almotriptan. The choice of dose should therefore be made on an individual basis.

* Almotriptan is not available in the 6.25 mg dose

If the headache returns, the dose may be repeated after 2 hours, but no more than two doses of 12.5 mg in total (maximum of 25 mg) should be given within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective. The safety of treating an average of more than four headaches in a 30-day period has not been established.

The maximum recommended dose of almotriptan should not be exceeded.

OVERDOSAGE

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

Patients and volunteers receiving single oral doses of 100 to 150 mg of almotriptan did not experience significant adverse events. Some of the adverse events reported as a result of receiving single oral doses of 100 to 150 mg of almotriptan were somnolence, nausea, vomiting and chest discomfort. During the clinical trials, one patient ingested 62.5 mg in a five-hour period and another patient ingested 100 mg in a 38-hour period. Neither patient experienced adverse reactions.

Based on the pharmacology of 5-HT_1 agonists, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Overdose should be treated symptomatically and vital functions should be maintained. Clinical and electrocardiographic monitoring should be continued for at least 20 hours, even if clinical symptoms are not observed.

The effects of hemodialysis or peritoneal dialysis on plasma concentrations of almotriptan are unknown.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Almotriptan is a selective 5-hydroxytryptamine$_{1B/1D}$ (5-$HT_{1B/1D}$) receptor agonist. Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors. Almotriptan has a weak affinity for 5-HT_{1A} and 5-HT_7 receptors, but has no significant affinity or pharmacological

activity at 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6; alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK_1, NK_2, NK_3) binding sites. The exact mechanism of action of almotriptan in humans is unknown.

Pharmacodynamics

Current theories on the etiology of migraine headaches suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from the sensory nerve endings in an activated trigeminal system. The therapeutic activity of almotriptan 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 the nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of the neuropeptide release, and reduced transmission in the trigeminal pain pathways.

Pharmacokinetics

Absorption: Almotriptan is well absorbed following oral administration. The mean oral absolute bioavailability is approximately 70%, and peak plasma concentrations of approximately 40 ng/mL are reached 1 to 3 hours after a single 12.5 mg dose. The rate and extent of absorption are not affected by food intake or by administration during a migraine attack. Almotriptan does not undergo substantial first-pass elimination.

Distribution: Almotriptan is extensively distributed. Almotriptan is minimally protein bound (approximately 35%), and the mean apparent volume of distribution is approximately 180 to 200 litres.

Metabolism: Almotriptan is metabolized by one minor and two major pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose) and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin mono-oxygenase is the minor route. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

Excretion: The mean half-life of almotriptan is between 3 and 4 hours. The primary route of elimination is via renal clearance, accounting for 75% of the administered dose. Approximately 40% of an administered dose is excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

Special Populations and Conditions

Paediatrics

Adolescents (12-17 years of age)

A pharmacokinetics study of almotriptan was conducted in adolescents (12 to 17 years) and adults (18 to 55 years) with or without a history of migraine with eighteen subjects in each group. No differences were observed in the rate or extent of absorption of almotriptan in adolescents compared with adults. Weight-corrected almotriptan clearance was higher in adolescents, which offset the increase in exposure expected on the basis of their lower body weights.

Children (< 12 years old)

No data are available for paediatrics under 12 years of age. Almotriptan is not indicated for use in this population (see INDICATIONS).

Geriatrics: Renal and total clearance and amount of drug excreted in the urine (10 L/h, 33 L/h and 30% respectively) were lower in elderly non-migraineur volunteers (aged 65 to 76 years) than in younger non-migraineur volunteers (aged 19 to 34 years), resulting in longer terminal half-life (3.7 h vs. 3.2 h) and higher area under the plasma concentration-time curve (405 ng.h/mL vs. 325 ng.h/mL) in the elderly subjects. However, the differences do not appear to be clinically significant.

Gender: No significant gender differences have been observed in pharmacokinetic parameters. Pharmacokinetic parameters of almotriptan between the genders have not been studied in adolescents 12 to17 years of age.

Race: No significant differences have been observed in the pharmacokinetic parameters between Caucasian and African-American adult volunteers. Pharmacokinetic parameters of almotriptan among the different races have not been studied in adolescents 12 to17 years of age.

Hepatic Insufficiency: The pharmacokinetics of almotriptan have not been assessed in this population. Based on the known mechanisms of the clearance of almotriptan, the maximum decrease in expected almotriptan clearance due to hepatic impairment would be 60% (see DOSAGE AND ADMINISTRATION and Hepatic Impairment in WARNINGS AND PRECAUTIONS).

Renal Insufficiency: The clearance of almotriptan was approximately 65% lower in adult patients with severe renal impairment (Cl/F = 19.8 L/h; creatinine clearance between 10 and 30 mL/min) and approximately 40% lower in patients with moderate renal impairment (Cl/F = 34.2 L/h; creatinine clearance between 31 and 71 mL/min) compared to healthy volunteers. Maximum plasma concentrations of almotriptan increased by approximately 80% in these patients (see DOSAGE AND ADMINISTRATION and Renal Impairment in WARNINGS AND PRECAUTIONS). Pharmacokinetic parameters of almotriptan have not been studied in adolescents 12 to17 years of age with renal insufficiency.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C)

DOSAGE FORMS, COMPOSITION AND PACKAGING

Almotriptan (almotriptan malate) tablet is available through prescription only. Almotriptan 12.5 mg tablet contains12.5 mg of almotriptan and is a white to off-white, round, biconvex film coated tablets with '12.5' debossed on one side and plain on other side.

The non-medicinal ingredients are: hypromellose, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, sodium stearyl fumarate, and titanium oxide.

The 12.5 mg tablets are available in a unit dose (aluminum blister pack) of 6 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

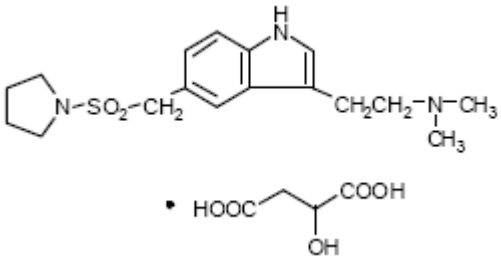
Common name: almotriptan malate

Chemical name: 1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]-methyl]-sulfonyl]-pyrrolidine-hydroxybutanedioate

Molecular formula: $C_{17}H_{25}N_3O_2S$-$C_4H_6O_5$

Molecular mass 469.56 g/mol

Structural formula:



Physicochemical properties: A white to slightly yellow crystalline powder.

Solubility: Freely soluble in water and methanol but practically insoluble in ethanol and methylene chloride.

pKa: 9.3 at 25°C

Melting Point: 167 – 173°C

pH: 1% solution in purified water has pH 4.1

Partition Coefficient: A partition coefficient of (-) 0.4 between octanol and water.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative, randomised, single dose, crossover bioequivalence study of Almotriptan 12.5 mg (almotriptan as almotriptan malate) tablets and Axert® 12.5 mg (almotriptan as almotriptan malate) tablets in forty (40) healthy subjects (25 male and 15 female; between the ages of 18 and 45), was conducted under fasting conditions. A summary of the bioavailability data is presented in the table below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Almotriptan malate (1 x 12.5 mg tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	287.06 291.92 (18.61)	279.91 283.82 (16.90)	102.55%	100.41% to 104.74%
AUC_{0-inf} (ng·h/mL)	295.16 300.13 (18.61)	288.78 292.92 (17.07)	102.21%	100.07% to 104.39%
C_{max} (ng/mL)	43.52 44.78 (23.81)	42.38 43.30 (22.01)	102.68%	97.08% to 108.60%
T_{max} € (h)	1.90 (59.88)	1.74 (63.53)		
$T_{½}$ § (h)	5.04 (13.23)	5.25 (18.83)		

* Almotriptan 12.5 mg tablets (manufactured for Pro Doc Ltée.)
† Axert 12.5 mg tablets (McNeil Consumer Healthcare, Canada) were purchased in Canada.
€ Expressed as the median (range) only
§ Expressed as the arithmetic mean (CV %) only

The pharmacological activity of almotriptan in the treatment of migraine has been assessed in Phase II and Phase III clinical trials.

Study demographics and trial design

Adults (> 18 years of age)

The efficacy of almotriptan was established in 3 multi-center, randomized, double-blind, placebo-controlled trials. Patients enrolled in these studies were primarily female (86%) and Caucasian (more than 98%), with a mean age of 41 years (range of 18 to 72) (see Table 4). Patients were instructed to treat a moderate to severe migraine headache. Two hours after taking one dose of study medication, patients evaluated their headache pain. If the pain had not decreased in severity to mild or to no pain, the patient was allowed to take an escape medication. If the pain had decreased to mild or to no pain at 2 hours but subsequently increased in severity between 2 and 24 hours, it was considered a relapse and the patient was instructed to take a second dose of study medication. Associated symptoms of nausea, vomiting, photophobia, and phonophobia were also evaluated.

In these studies, the percentage of patients achieving a response (mild or no pain) 2 hours after treatment was significantly greater in patients who received either almotriptan 6.25 mg or 12.5 mg, compared with those who received placebo. A higher percentage of patients reported pain relief after treatment with the 12.5 mg dose than with the 6.25 mg dose. Doses greater than 12.5 mg did not lead to significantly better response. These results are summarized in Tables 4 to 6.

Table 4 Summary of patient demographics for clinical trials in adult patients

Study #	Placebo	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
1-3 (Adults)	multi-center, randomized, double-blind, placebo-controlled	6.25 mg & 12.5 mg, oral over 24 hours	1602 (88% of subjects completed study)	41 (18-72)	M/F

Study results

Adults

The efficacy of almotriptan was established in 3 multi-center, randomized, double-blind, placebo-controlled European trials. Patients enrolled in these studies were primarily female (86%) and Caucasian (more than 98%), with a mean age of 41 years (range of 18 to 72). Patients were instructed to treat a moderate to severe migraine headache. Two hours after taking one dose of study medication, patients evaluated their headache pain. If the pain had not decreased in severity to mild or to no pain, the patient was allowed to take an escape medication. If the pain had decreased to mild or to no pain at 2 hours but subsequently increased in severity between 2 and 24 hours, it was considered a relapse and the patient was instructed to take a second dose of study medication. Associated symptoms of nausea, vomiting, photophobia, and phonophobia were also evaluated.

In these three studies, the percentage of patients achieving a response (mild or no pain) 2 hours after treatment was significantly greater in patients who received either almotriptan 6.25 mg or 12.5 mg, compared with those who received placebo. In study 1, Almotriptan 12.5 mg was superior to placebo as early as 30 minutes after drug administration (pairwise comparison, p = 0.0485). A higher percentage of patients reported pain relief after treatment with the 12.5 mg dose than with the 6.25 mg dose. Doses greater than 12.5 mg did not lead to significantly better response. These results are summarized in Tables 5-7.

Table 5 Results of study 1 in adult patients

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo
patients achieving a response (mild or no pain) 2 hours after treatment	6.25 mg – 56.3%* (n = 167) 12.5 mg – 58.5%† (n = 164)	32.5% (n = 80)

* *p* value 0.002 in comparison to placebo
† *p* value < 0.001 in comparison to placebo

Table 6 Results of study 2 in adult patients

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo
patients achieving a response (mild or no pain) 2 hours after treatment	12.5 mg – 56.5%‡ (n = 184)	42.4% (n = 98)

‡ *p* value 0.008 in comparison to placebo

Table 7 Results of study 3 in adult patients

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo
patients achieving a response (mild or no pain) 2 hours after treatment	6.25 mg – 57.3% (n = 360) 12.5 mg – 64.6%† (n = 373)	33.9% (n = 176)

† *p* value < 0.001 in comparison to placebo

These results cannot be validly compared with results of anti-migraine treatments in other studies. 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 responses and the timing of responses may be expected to vary considerably from study to study.

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

Two to 24 hours following the initial dose of study medication, patients were allowed to take an escape medication or a second dose of study medication for pain response.

Escape medication was taken more frequently by patients in the placebo groups than by those in the active almotriptan treatment groups.

The efficacy of almotriptan was unaffected by the presence of aura; by gender, weight, 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 effect of race on efficacy.

Adolescents (12-17 years)
The efficacy of almotriptan malate tablets in adolescent patients was evaluated in a double-blind, randomized, placebo-controlled study of 42 days in duration with 4 treatment arms (almotriptan 6.25 mg, 12.5 mg, 25 mg and placebo). Patients enrolled in this study had at least a one-year history of migraine attacks with or without aura, experienced 1-6 moderate attacks per month, were primarily female (60%) and Caucasian (75%). Approximately 80% of the patients in both placebo and almotriptan arms completed the study. Patients were instructed to take their dose of study medication as soon as possible and no more than 4 hours after a moderate to severe migraine attack. Two hours after taking one dose of study medication, patients evaluated their headache pain. Migraine-associated symptoms of nausea, photophobia, and phonophobia were also evaluated.

In this study, the percentages of patients achieving pain relief 2 hours after treatment were statistically significantly greater for each of the 3 almotriptan arms compared to placebo. The 2-hour pain relief results for the 6.25 and 12.5 mg dose groups are summarized in Table 8. The 25 mg dose provided no added improvement for pain relief.

Table 8 Response Rates 2 Hours Following Treatment of Initial Headache

Study#	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg
1	55.3% 94/170 patients	71.8%* 127/177 patients	72.9%† 132/181 patients

* *p* value 0.001 in comparison with placebo
† *p* value <0.001 in comparison with placebo

Although not statistically significant, there was a decreased incidence of migraine-associated photophobia and phonophobia following administration of almotriptan 6.25 mg and 12.5 mg compared with placebo.

DETAILED PHARMACOLOGY

Almotriptan was developed with the aim of producing a more specific 5-$HT_{1B/1D}$ agonist that would have an improved efficacy and adverse event profile. The pharmacology of almotriptan has been assessed *in vitro* in human artery tissue. *In vitro*, almotriptan was superior to sumatriptan, in both the capacity to induce, as well as the affinity for, vasoconstriction in human meningeal arteries. In addition, almotriptan has been shown to have a higher affinity for meningeal artery tissue than pulmonary or coronary artery tissue. The affinity of almotriptan for human meningeal artery tissue was three times greater than that of sumatriptan. The relevance of these *in vitro* data to the clinical safety of almotriptan is not known.

The affinity of almotriptan for the serotonergic receptors, namely 5-HT_{1B} and 5-HT_{1D}, was demonstrated by radioligand displacement in membrane preparations. Additional receptor binding studies extended the characterization of almotriptan binding to other receptor subtypes, the only significant binding occurring at non-selective muscarinic receptors, and opiate receptors. Almotriptan displayed little or no affinity for CGRP, dopamine D_1 or D_2, endothelin, tachykinin, or histamine receptors. It was also inactive on adenosine, norepinephrine and serotonin uptake sites.

Based upon data from dose finding studies, the 6.25 and 12.5 mg doses were selected as the safest and most effective for relief of migraine pain and associated symptoms. Two studies evaluated the effect of almotriptan on vascular resistance, heart rate and blood pressure in anesthetized cats, and showed no consistent changes in either mean blood pressure or heart rate up to doses of 3 mg/kg, although some transient rises in blood pressure were observed. An increase in carotid vasculature resistance (276% of baseline) was observed along with a decrease in blood flow (72% of baseline).

Almotriptan was also shown to induce a dose-dependent decrease in blood flow through the arteriovenous anastomoses.

TOXICOLOGY

Acute Toxicity

Single-dose toxicity studies were conducted in rats and mice by oral, intravenous and subcutaneous routes. Single oral doses of almotriptan caused mortality at 2000 mg/kg in both mice and rats, but 1000 mg/kg was a non-lethal dose. Clinical signs included palpebral ptosis, tremors, abnormal gait, mydriasis (rats) and clonic convulsions, which generally preceded death. Gross findings of injection site irritation were noted in both mice and rats after subcutaneous doses.

Chronic Toxicity

The central nervous and cardiovascular systems were the primary organ systems affected by the toxicity of almotriptan. Central nervous system and related clinical signs were noted in rats at oral doses of 100 mg/kg or greater. Dogs were more sensitive, with signs and symptoms being

noted at 2 mg/kg/day and higher. In a 4-week oral study, dogs had numerous clinical signs approximately 1 hour after dosing including mydriasis; splayed and/or stiff hind limbs; unsteadiness on the feet; vocalization; rapid heart rate; hyperactivity; hypersensitivity to external stimuli; tremors; circling; nervous, excited or aggressive behaviour; increased respiratory rate and lacrimation. The incidence and severity of the clinical signs appeared to be dose-related. The sensitivity of dogs to the CNS effects of triptans has been observed with other drugs.

Cardiovascular findings in both male and female dogs were increases in heart rate within 1 hour after dosing by oral, subcutaneous or intravenous routes. Histologic changes in the thyroid gland were seen in rats administered almotriptan at oral doses of 400 mg/kg/day or greater. Minor hematology, clinical chemistry or urinalysis changes in rats and dogs were reported as possibly related to almotriptan treatment. However, no drug-related gross or microscopic lesions could be correlated to these changes.

Nursing Mothers
Lactating rats dosed with almotriptan had milk levels equivalent to maternal plasma levels at 0.5 hours and 7 times higher than plasma levels at 6 hours after dosing.

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PART III: CONSUMER INFORMATION
Pr ALMOTRIPTAN
(Almotriptan tablets)

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

ABOUT THIS MEDICATION

What the medication is used for:
Almotriptan (almotriptan malate) tablet is a medication used for acute treatment of migraines with or without aura in adults and adolescents aged 12 – 17 years. **Almotriptan is not for use in children under 12 years of age.** Almotriptan should not be used continuously to prevent or reduce the number of attacks you experience. Almotriptan is a member of a class of drugs called selective 5-$HT_{1B/1D}$ receptor agonists.

Tell your doctor about your symptoms. Your doctor will decide if you have migraines. Use Almotriptan only for a migraine attack. Almotriptan should not be used to treat headaches that might be caused by other, more serious conditions.

You will find more information about migraine at the end of this leaflet.

What is migraine and how does it differ from other headaches?
Migraine is an intense, throbbing, typically one-sided headache that often includes nausea, vomiting, sensitivity to light, and sensitivity to sound. According to many migraine sufferers, the pain and symptoms from a migraine headache are more intense than the pain and symptoms of a common headache.

Some people may have visual symptoms before the headache, such as flashing lights or wavy lines, called an aura.

Migraine attacks typically last for hours or, rarely, for more than a day, and they can return frequently. The severity and frequency of migraine attacks may vary.

Based on your symptoms, your doctor will decide whether you have a migraine.

Who gets migraines?
Migraine headaches tend to occur in members of the same family. Both men and women get migraine, but it is more common in women.

What may trigger a migraine attack?
Certain things are thought to trigger migraine attacks in some people. Some of these triggers are:

- Certain foods or beverages (e.g. cheese, chocolate, citrus fruit, caffeine, alcohol)
- Stress
- Change in behaviour (e.g. under/oversleeping; missing a meal; change in diet)
- Hormonal changes in women (e.g. menstruation)

You may be able to prevent migraine attacks or diminish their frequency if you understand what specifically triggers your attacks. Keeping a headache diary may help you identify and monitor the possible migraine triggers you encounter. Once the triggers are identified, you and your doctor can modify your treatment and lifestyle appropriately.

What it does:
Migraine headache is believed to be caused by a widening of the blood vessels in the head. Almotriptan narrows the vessels and relieves the pain and other symptoms of migraine headache.

When it should not be used:
Do not take Almotriptan if you have:

- had a serious allergic reaction to Almotriptan or any of its ingredients;
- uncontrolled high blood pressure;
- heart disease or history of heart disease.
- severe liver disease

Almotriptan should not be used within 24 hours of treatment with another 5-$HT_{1B/1D}$ agonist, such as naratriptan (Amerge®), rizatriptan (Maxalt®), sumatriptan (Imitrex®), or zolmitriptan (Zomig®); or ergotamine type medications such as ergotamine (Bellergal® Spacetabs®, Cafergot®, Ergodryl™), dihydroergotamine (Dihydroergotamine (DHE), Migranal®), or methysergide (Sansert®). (The brands listed are the trademarks of their respective owners and are not trademarks of Canada Inc.)

What the medicinal ingredient is:
Almotriptan (as almotriptan malate)

What the important nonmedicinal ingredients are:
hypromellose, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, sodium stearyl fumarate, and titanium oxide.

What dosage forms it comes in:
Tablets: 12.5 mg

WARNINGS AND PRECAUTIONS

BEFORE you use Almotriptan talk to your doctor or pharmacist if you:

- Have past or present medical problems
- Have a history of high blood pressure, chest pain, shortness of breath, strokes, or heart disease
- Have risk factors for heart disease, such as:
  - High blood pressure or diabetes
  - High cholesterol
  - Obesity
  - Smoking
  - Family history of heart disease
  - You are a post-menopausal woman
  - You are a male over 40 years of age
- Have or have had allergies

- Have or have had allergic reactions to sulfonamides, also known as sulfa drugs (ask your doctor if you are not sure what sulfonamide drugs are)
- Have kidney or liver disease
- Plan to become or are already pregnant
- Plan to breastfeed, or if you are already breastfeeding an infant
- Plan to take or are taking drugs, including those obtained without a prescription, and those you normally take for a migraine.

Do not use Almotriptan if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Almotriptan include:
- Other drugs in the same class
- Ergotamine-type medications
- Monoamine oxidase inhibitors (MAOIs)
- Ketoconazole, itraconazole, ritonavir or erythromycin
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- Herbal products that contain St. John's Wort (*Hypericum perforatum)*

Do not take Almotriptan with any other drug in the same class within 24 hours, such as naratriptan (Amerge®), rizatriptan (Maxalt®), sumatriptan (Imitrex®), or zolmitriptan (Zomig®).

Do not take Almotriptan within 24 hours of taking ergotamine-type medications such as ergotamine (Bellergal® Spacetabs®, Cafergot®, Ergodryl™), dihydroergotamine (Dihydroergotamine (DHE), Migranal®), or methysergide (Sansert®) to treat your migraine.

Tell your doctor if you are taking monoamine oxidase (MAO) inhibitors, such as phenelzine sulfate (Nardil™), moclobemide (Manerix®) or tranylcypromine sulfate (Parnate®) for mental depression, or if it has been less than two weeks since you stopped taking a MAO inhibitor.

Tell your doctor if you are taking ketoconazole (Nizoral®, Apo®-Ketoconazole, Novo-Ketoconazole), itraconazole (SPORANOX®), ritonavir (Norvir®), or erythromycin (Apo®-Erythro, Diomycin®, Erybid™, Eryc®, Erythrocin®, Erythromid®, Novo-Rythro Encap, PCE®, PMS-Erythromycin), or if it has been less than one week since you stopped taking one of these drugs.

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

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor has prescribed a 12.5 mg dose of Almotriptan for your migraine attack. When you have a migraine headache, take your medication as directed by your doctor. If your headache comes back after your initial dose, you may take a second dose any time **after 2 hours** of administering the first dose. If you had no pain relief after the first dose, do **not** take a second dose without first consulting with your doctor. Do not take more than 25 mg of Almotriptan in a 24-hour period (for example, do not take more than two 12.5 mg tablets in 24 hours). If your condition worsens, seek medical attention.

Overdose:
If you take more medication than you have been told to take, you should contact your doctor, hospital emergency department, or nearest poison control centre immediately, even if you do not feel sick.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all prescription drugs, Almotriptan can cause side effects. In studies, Almotriptan was generally well tolerated. The side effects were usually mild and temporary. The following is **not** a complete list of side effects reported with Almotriptan. Do not rely on this leaflet alone for information about side effects. Ask your doctor to discuss with you the more complete list of side effects.

In studies, the **most common** side effects reported were:
- Nausea
- Sleepiness
- Dizziness
- Tingling sensation
- Headache
- Dry mouth

Other side effects that may rarely occur include: shortness of breath, wheeziness, heart throbbing, increased blood pressure, fast heart rate or irregular heart rate.

If any of these occur, do not take any more Almotriptan and contact your doctor immediately.

If you experience sleepiness after taking Almotriptan, you should not perform complex tasks such as driving or operating heavy

machinery until you are sure you are no longer sleepy or drowsy.

Call your doctor immediately if you feel tightness, pain, pressure or heaviness in your chest, throat, neck or jaw after taking Almotriptan. Do not take Almotriptan again until your doctor has checked you.

Call your doctor immediately if you feel unwell or have any other symptoms that you do not understand or find distressing while taking Almotriptan.

Call your doctor immediately if you experience any symptoms that suggest an allergic reaction (such as a rash or itching) after taking Almotriptan.

This is not a complete list of side effects. For any unexpected effects while taking Almotriptan contact your doctor or pharmacist.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug, call and seek urgent medical attention
		Only if severe	In all cases	
Rare	Shortness of breath, wheeziness, heart throbbing, increased blood pressure, fast heart rate or irregular heart rate.			✓
Very rare	Tightness, pain, pressure or heaviness in your chest, throat, neck or jaw.			✓
Very rare	Allergic reaction (swelling of the eyelids, face, or lips; skin rash, itchy rash, skin lumps or hives).			✓

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. It could be harmful to children. Store your medication at room temperature (15°C to 30°C). If your medication has expired, throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to do so. Throw away your medicine as instructed. Be sure that discarded tablets are out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

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Last revised: August 9, 2017