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For detailed instructions regarding style and layout refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained on the website http://www.icmje.org. Articles should be submitted under conventional headings of introduction, methods and materials, results, discussion, but other headings will be considered if more suitable and papers should be double-spaced. For Uniform Requirements for Sample References go to http://www.nlm.nih.gov/ bsd/uniform_requirements.html.

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Acknowledgements

Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text. The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

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Titles of journals should be abbreviated according to the style used in Index Medicus. References should list the names of up to six authors; if there are more, cite the first SIX, then et al.

Provide the full title, year of publication, volume number and inclusive pagination for journal articles. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text.

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INFORMATION FOR AUTHORS / SUBMISSION PROCESS

(continued)

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For Reference Guidelines
www.nlm.nih.gov/bsd/uniform_requirements.html

Examples of correct forms of reference:

Journals

1. Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Tables

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Neuroimaging Highlights require a figure of several panels that clearly outlines all features of the relevant imaging. For example, for MR images this may require different cuts and sequences, etc. Combining more than one imaging modality strengthens the report. The report may also benefit from a single additional panel in a figure if it is directly relevant, e.g. a pathological image or patient image. The text should include a very brief discussion of the case history confined to the relevant history, pertinent abnormal findings, and clinical course with outcome. An additional one to two paragraphs should briefly describe the neuroimaging panels present, and very briefly review relevant aspects of the literature. Overall, the Neuroimaging Highlight should be 500 words or less, with no more than 10 references.

Images should be of the highest quality, submitted electronically as a tiff or jpeg file at a minimum of 300 dpi and at a size large enough for the printed journal (i.e. not less than 2" wide).

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THE CANADIAN JOURNAL OF
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The Canadian Journal of Neurological Sciences is the official publication of the four member societies of the Canadian Neurological Sciences Federation (CNSF). The Journal is a widely circulated internationally recognized medical journal that publishes peer-reviewed articles by-monthly.

History

The first Canadian Journal of Neurological Sciences (CJNS) was published in 1974 in Winnipeg. In 1981, the Journal became the official publication of the member societies of the CNSF.

The Journal Today

Today, the Journal continues to encourage the publication of papers from all branches of the neurosciences. Journal policy is based on the firm belief that specialists working on the nervous system share many common interests and have important ideas to communicate to each other. The Journal publishes original work in both the clinical and basic neurosciences. The circulation is currently 1,600 and consists of society members, non-members and institutions in Canada, the United States and abroad.

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The Journal Editorial Board wants to include high quality clinical and basic neuroscience research that occurs in Canada and abroad. The Editor-in-Chief and the board encourage authors to send the final version of their work to the Journal for possible publication. All submissions received by the Journal undergo detailed and careful peer-reviewed scrutiny.

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CALENDAR OF EVENTS

May 7-9, 2009
Vancouver, British Columbia, Canada
International Vocational Outcomes in Traumatic Brain Injury Conference 2009
For information go to: www.tbicvancouver.com

May 10-13, 2009
Ottawa, Ontario, Canada
2nd Annual Canadian Network for Innovation in Education (CNIE) International Conference 2009
For more information please visit the 2009 International Conference website at www.learningconference.ca.

May 15, 2009
Sydney, Nova Scotia, Canada
Neurology Update VII
For more information contact Marlene Weaver R.N. 902-567-7930 or email weaverm@cbdha.nshealth.ca

June 9 - 12, 2009
Halifax, Nova Scotia, Canada
44th Annual Congress of the Canadian Neurological Sciences Federation
For more information go to: www.cnsfederation.org or contact the secretariat office at (403) 229-9544.

June 9-12, 2009
Halifax, Nova Scotia, Canada
Matters of the Brain - CANN 40th Annual Meeting and Scientific Sessions
For more information go to: www.cann.ca/cann_conf.php or contact the secretariat office at (403) 229-9544.

June 10-13, 2009
Daegu, Korea
10th Asian & Oceanian Congress of Child Neurology
For registration, hotel information and other information go to www.aoccn2009.com.

July 8-10, 2009
Toronto, Ontario, Canada
SickKids Centre for Brain & Behaviour 1st Annual International Symposium: Brain Injury in Children
Visit www.sickkids.ca/learninginstitute or email li.conferences@sickkids.ca.

June 18-21, 2009
Toronto, Ontario, Canada
26th International Congress of Chemotherapy and Infection
Register on-line now at: www.occ-09.com or email icc09@congresscan.com

July 17-18, 2009
St. John's, Newfoundland, Canada
Canadian Radiosurgery Society Meeting (CaRS)
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August 26-29, 2009
Boston, Massachusetts, USA
6th Annual World Congress for Brain Mapping and Image Guided Therapy
Call for Papers - Abstract Submission Deadline: March 27, 2009.
For more information go to: www.ibmisps-worldcongress.org

August 27-30, 2009
Munich, Germany
1st International Congress on Clinical Neuroepidemiology
For information about our Congress, please go to our website: www.neuro2009.com.

August 30-September 4, 2009
Boston, Massachusetts, USA
XIV Congress of the World Federation of Neurosurgical Societies (WFNS)
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September 11-12, 2009
Toronto, Ontario, Canada
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September 12-15, 2009
Florence, Italy
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For additional information, please visit our web-site: www.efns.org/efns2009 or e-mail florence2009@efns.org.

September 16-19, 2009
Maastricht, the Netherlands
9th Congress of the European Association of NeuroOncology
For additional information: Website: www.eano.eu

October 1 - 3, 2009
Toronto, Ontario, Canada
5th Canadian Conference on Dementia
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October 8-11, 2009
Prague, The Czech Republic
3rd World Congress on Controversies in Neurology (CONy)
For more information please visit our site: comtecmed.com/cony/2009

October 9 - 10, 2009
Zenith of Rouen, France
1st European Congress on Environmental Pathologies
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October 15-16, 2009
Valencia, Spain
International Symposium on Neurorehabilitation. From Basics to Future
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Maxalt®

rizatriptan benzoate tablets

Maxalt RPD®

rizatriptan benzoate wafers

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: 5-HT$_1$ Receptor Agonist

INDICATIONS AND CLINICAL USE

Adults

MAXALT® is indicated for acute treatment of migraine attacks with or without aura in adults. MAXALT® is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS in the Supplemental Product Information section). Safety and effectiveness of MAXALT® have 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 MAXALT® 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 MAXALT® 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).

Special Populations

For use in special populations, see Supplemental Product Information, WARNINGS AND PRECAUTIONS, Special Populations.

CONTRAINDICATIONS

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

MAXALT® is contraindicated within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT® 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, MAXALT® is contraindicated in patients with severe hepatic impairment.

MAXALT® is contraindicated in patients who are hypersensitive to rizatriptan or any component of the formulation.

Safety Information

WARNINGS AND PRECAUTIONS

General

MAXALT® 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 MAXALT® (see ADVERSE EVENTS). Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that MAXALT® does not adversely affect them.

Cardiovascular

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

MAXALT® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT$_1$ agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of other 5-HT$_1$ agonists, and may therefore also occur with MAXALT®. Because of the potential of this class of compounds (5-HT$_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT® should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that MAXALT® 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, MAXALT® 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 MAXALT®, 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 MAXALT® who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluation as they continue to use MAXALT®.

If symptoms consistent with angina occur after the use of MAXALT®, 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 MAXALT®.

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 MAXALT® administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS).

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists

MAXALT® 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-HT$_1$ agonists. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience with MAXALT®

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 MAXALT®, 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 MAXALT®

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

Cerebrovascular Events and Fatalities Associated with 5-HT$_1$ Agonists

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT$_1$ agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with MAXALT® 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-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 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

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(~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 MAXALT®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Other Vasospasm-Related Events

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive postmarket experience has shown the use of another 5-HT_1 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-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT® (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, MAXALT® 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

Phenylketonurics

Phenylketonuric patients should be informed that MAXALT RPD® Wafers contain phenylalanine (a component of aspartame). Each 5 mg wafer contains 1.05 mg phenylalanine, and each 10 mg wafer contains 2.10 mg phenylalanine.

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 in the Product Monograph 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-HT_1 agonists such as MAXALT®. 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, MAXALT® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 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-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 MAXALT®.

Seizures

Caution should be observed if MAXALT® 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 MAXALT® in patients with or without risk factors or previous history of seizures (see ADVERSE REACTIONS, Post-Marketing Adverse Reactions, Nervous System in the Supplemental Product Information).

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 in the Product Monograph, 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 MAXALT® 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

For use in special populations, see Supplemental Product Information, WARNINGS AND PRECAUTIONS, Special Populations.

ADVERSE REACTIONS

(see Supplemental Product Information for full listing)

Adverse Drug Reaction Overview

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

Long-Term Safety

In long-term extension studies, a total of 1854 patients treated 16,150 migraine attacks with MAXALT® 5 mg Tablets and 24,043 attacks with MAXALT® 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 MAXALT® 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 MAXALT® in causation cannot be reliably determined.

To report a suspected adverse reaction, please contact Merck Frosst Canada Ltd. by:

Toll-free telephone: 1-800-567-2594
Toll-free fax: 1-877-428-8675
By regular mail: Merck Frosst Canada Ltd., P.O. Box 1005, Pointe-Claire – Dorval, QC H9R 4P8

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 MAXALT® 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 MAXALT® (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Other 5-HT_1 Agonists

The administration of rizatriptan with other 5-HT_1 agonists has not been evaluated in migraine patients.

Because their vasospastic effects may be additive, co-administration of rizatriptan and other 5-HT_1 agonists within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

Propranolol

MAXALT® 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

In a pharmacokinetic study with paroxetine and rizatriptan, paroxetine had no influence on the plasma levels of rizatriptan and no symptoms of serotonin syndrome emerged. Cases of life-threatening serotonin syndrome have however 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).

Food

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, MAXALT® was administered without regard to food.

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Administration

DOSAGE AND ADMINISTRATION

(see Product Monograph for complete information)

Dosing Considerations

MAXALT® is recommended only for the acute treatment of migraine attacks. MAXALT® 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

MAXALT® Tablets and MAXALT RPD® Wafers

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 CLINICAL TRIALS in the Product Monograph). 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.

For MAXALT RPD® Wafers, administration with liquid is not necessary. The wafer is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the wafer placed on the tongue, where it will dissolve and be swallowed with the saliva.

Redosing

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

Patients receiving propranolol

A single 5 mg dose of MAXALT® 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 m^2), the AUC of rizatriptan was approximately 44% greater than in patients with normal renal function (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph). Consequently, if treatment is deemed advisable in these patients, the 5 mg MAXALT® Tablet or Wafer 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

MAXALT® 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 ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph). Consequently, if treatment is deemed advisable in the presence of moderate hepatic impairment, the 5 mg MAXALT® Tablet or Wafer 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

MAXALT® 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.

Missed Dose

If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

OVERDOSAGE

No overdoses of MAXALT® 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 MAXALT®. The elimination half-life of rizatriptan is 2 to 3 hours (see ACTION AND CLINICAL PHARMACOLOGY in the Product Monograph). 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.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Special Populations

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 MAXALT® is administered to women who are breast-feeding. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatrics (< 18 years of age): MAXALT® 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 MAXALT® Tablets (5 mg) was not different from that of placebo (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the product monograph).

Geriatrics (> 65 years of age): The safety and effectiveness of MAXALT® 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 MAXALT® 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:

MAXALT® should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the product monograph).

Monitoring and Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT®.

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 MAXALT®

Typical 5-HT_1 Agonist Adverse Reactions

As with other 5-HT_1 agonists, MAXALT® 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 MAXALT® Tablets. The most common adverse events during treatment with MAXALT® 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 ≥ 1% and greater than placebo) after a single dose of MAXALT® Tablets and MAXALT RPD® 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 (≥ 1% and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT® Tablets or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials†

	% of Patients		
	Placebo	MAXALT® 5 mg	MAXALT® 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 (≥ 1% and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT RPD® Wafers or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials†

	% of Patients		
	Placebo	MAXALT RPD® 5 mg	MAXALT 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
Hypesthesia	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.

MAXALT® 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.

Other Events Observed in Association with the Administration of MAXALT®

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 MAXALT® in their causation cannot be reliably

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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 MAXALT® 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 MAXALT®. 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 glosodynia.

Metabolic

Infrequent was dehydration.

Musculoskeletal

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

Neurological/Psychiatric

Frequent were hypesthesia 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.

The adverse experience profile seen with MAXALT RPD® Wafers was similar to that seen with MAXALT® Tablets.

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.

Musculoskeletal: facial pain.

Special Senses: Dysgeusia.

Nervous System: serotonin syndrome.

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

Drug Abuse and Dependence

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

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Cymbalta® DELAYED RELEASE duloxetine HCl CAPSULES

30 mg and 60 mg Delayed-release Capsules

Prescribing Summary

Patient Selection Criteria

Analgesic

INDICATIONS

CYMBALTA® (duloxetine hydrochloride) is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

CONTRAINDICATIONS

CYMBALTA® is contraindicated in patients with a known hypersensitivity to the drug or the other components of the product.

Monoamine Oxidase Inhibitors (MAOIs)
CYMBALTA® should not be used concomitantly with a monoamine oxidase inhibitor (MAOI), including linezolid, an antibiotic which is a non-selective reversible MAOI or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping CYMBALTA® before starting an MAOI.

Hepatic Impairment
CYMBALTA® is contraindicated in patients with any liver disease resulting in hepatic impairment.

Uncontrolled Narrow-angle Glaucoma
In clinical trials, CYMBALTA® was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

Severe Renal Impairment
CYMBALTA® is contraindicated in patients with severe renal impairment (i.e. creatinine clearance <30 mL/min) or end-stage renal disease.

Thioridazine
Concomitant use of CYMBALTA® and thioridazine is contraindicated.

CYP1A2 Inhibitors
CYMBALTA® should not be used concomitantly with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin or enoxacine).

USE IN SPECIAL POPULATIONS

Use in Pregnant Women:
Safe use of CYMBALTA® during pregnancy has not been established. Therefore, CYMBALTA® should not be administered to pregnant women or those intending to become pregnant, unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus.

When treating a pregnant woman with CYMBALTA® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. There are no adequate and well-controlled studies in pregnant women. In animal reproductive studies, duloxetine has been shown to have adverse effects on embryo/fetal and post-natal development. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

The effect of duloxetine on labour and delivery in humans is unknown. However, because of the possibility that duloxetine and/or its metabolites may have adverse effects on the newborn, duloxetine should be used during labour and delivery only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Women:
Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on CYMBALTA® is not recommended. Patients should be advised to notify their physician if they are breast-feeding.

Use in Pediatrics (<18 years of age):
The safety and efficacy of CYMBALTA® in pediatric patients (<18 years of age) have not been established and its use in this patient population is not indicated.

Use in Geriatrics (≥65 years of age):
Of the 1429 CYMBALTA®-treated patients in the DPN studies, 31.9% (456) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Use in Patients with Substantial Alcohol Use:
Use of CYMBALTA® in patients who consume substantial amounts of alcohol may be associated with severe liver injury. Isolated cases of liver failure, including fatal cases, have been reported. CYMBALTA® should only be used in exceptional circumstances and with extreme caution in these patients.

Safety Information

WARNINGS AND PRECAUTIONS

Potential Association with Behavioural and Emotional Changes, Including Self-Harm

Recent analyses of pediatric placebo-controlled clinical trial safety databases from selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.

There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms
Patients currently taking SSRIs or newer antidepressants should NOT be discontinued abruptly due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

Monoamine Oxidase Inhibitors (MAOI):
The effects of combined use of CYMBALTA® and MAOIs have not been evaluated in humans or animals. Because CYMBALTA® is an inhibitor of both serotonin and norepinepherine reuptake, it is recommended that CYMBALTA® not be used in combination with a MAOI (including linezolid, an antibiotic which is a non-selective reversible MAOI), or within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping CYMBALTA® before starting a MAOI.

Hepatic Impairment:
Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. CYMBALTA® is contraindicated in patients with any liver disease resulting in hepatic impairment.

Hepatotoxicity:
CYMBALTA® increases the risk of elevation of serum aminotransferase levels. In clinical trials, the median time to detection of the aminotransferase elevation was about two months. In these patients, these were usually transient and self-limiting with continued use, or resolved upon discontinuation of CYMBALTA®. (SEE POST-MARKET ADVERSE DRUG REACTIONS)

CYMBALTA® should be used with caution in patients treated with other drugs associated with hepatic injury. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, CYMBALTA® should not ordinarily be prescribed to patients with substantial alcohol use.

Physicians should be aware of the signs and symptoms of liver damage (e.g. pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms) and should investigate such symptoms promptly. CYMBALTA® should be discontinued and should not be restarted in patients with jaundice.

Controlled Narrow-angle Glaucoma:
In clinical trials, CYMBALTA® was associated with an increased risk of mydriasis; therefore it should be used cautiously in patients with controlled narrow-angle glaucoma.

Thioridazine:
Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related. CYMBALTA® is a moderate inhibitor of CYP2D6 and increases the AUC and Cmax of drugs metabolized by CYP2D6. CYMBALTA® should not be used in combination with thioridazine.

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Inhibitors of CYP1A2:
Because CYP1A2 is involved in duloxetine metabolism, the potential exists for increased concentrations of duloxetine when co-administered with a CYP1A2 inhibitor. CYMBALTA® should not be used concomitantly with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin or enoxacine).

Sucrose:
CYMBALTA® capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Cardiovascular:

Blood Pressure and Heart Rate
CYMBALTA® has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. (SEE POST-MARKET ADVERSE DRUG REACTIONS IN SUPPLEMENTAL PRODUCT INFORMATION)

Blood pressure and heart rate should be evaluated prior to initiating treatment and periodically measured throughout treatment, especially in patients with known hypertension and/or other cardiac disease. CYMBALTA® should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when CYMBALTA® is used with drugs that may impair its metabolism. For patients who experience a sustained increase in blood pressure while receiving CYMBALTA® either dose reduction or gradual discontinuation should be considered.

Electrocardiogram Changes
CYMBALTA® has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's pre-marketing testing.

In DPN placebo-controlled clinical trials, CYMBALTA®-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients.

Concomitant Illness:
Clinical experience with CYMBALTA® in patients with concomitant systemic illnesses is limited. Caution is advisable when using CYMBALTA® in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (e.g. caution should be exercised in using CYMBALTA® in patients with conditions that slow gastric emptying).

Dependence:

Dependence Liability
In animal studies, duloxetine did not demonstrate stimulant or barbiturate-like (depressant) abuse potential.

While CYMBALTA® has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of CYMBALTA® (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

Discontinuation of Treatment:
Discontinuation symptoms have been systematically evaluated in patients taking CYMBALTA®. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in CYMBALTA®-treated patients compared with those discontinuing from placebo: dizziness, nausea, headache, paresthesia, vomiting, irritability, nightmare, fatigue, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo.

Patients should be monitored for these symptoms when discontinuing treatment with CYMBALTA®. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response.

Endocrine:

Glucose Regulation
In DPN trials, CYMBALTA® treatment worsened glycemic control in some diabetic patients. In three clinical trials of CYMBALTA® for the management of pain associated with DPN, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 9.8 mmol/L (176 mg/dL), and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, CYMBALTA® was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 0.67 mmol/L (12 mg/dL) in the CYMBALTA® group and decreased by 0.64 mmol/L (11.5 mg/dL) in the routine care group, which was statistically significantly different. HbA1c increased by 0.5% in the CYMBALTA® group and by 0.2% in the routine care groups.

Hematologic:

Abnormal Bleeding
There have been reports of bleeding abnormalities with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinepherine reuptake inhibitors (SNRIs), including very rare cases of ecchymoses and gastrointestinal bleeding reported with CYMBALTA®. While a causal relationship to CYMBALTA® has not been established, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences. Skin and other mucous membrane bleedings have been reported following treatment with CYMBALTA®. Caution is advised in patients taking anticoagulants (e.g. warfarin) and/or medicinal products known to affect platelet function (e.g. nonsteroidal anti-inflammatories and ASA), and in patients with known tendency for bleeding or those with predisposing conditions.

Neurologic:

Seizures
CYMBALTA® has not been systematically evaluated in patients with a seizure disorder. As with other CNS active drugs, CYMBALTA® should be used with caution in patients with a history of a seizure disorder.

Serotonin Syndrome/Neuroleptic Malignant Syndrome:
On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with CYMBALTA® should be discontinued if such events occur and supportive symptomatic treatment should be initiated. CYMBALTA® should not be used in combination with MAOIs (including linezolid, an antibiotic which is a non-selective reversible MAOI) or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (e.g. triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome.

Triptans (5HT1 Agonists)
Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinepherine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with CYMBALTA® and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Effects on the Ability to Drive and Use Machines:
CYMBALTA® may be associated with undesirable effects such as sedation and dizziness. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that CYMBALTA® therapy does not affect their ability to engage in such activities.

Psychiatric:

Suicide
As with other drugs with similar pharmacological action (e.g. SSRIs or SNRIs), isolated cases of suicidal ideation and suicidal behaviours have been reported during CYMBALTA® therapy or early after treatment discontinuation.

Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Activation of Mania/Hypomania
As with similar CNS active drugs, CYMBALTA® should be used cautiously in patients with a history of mania.

The decision to initiate symptomatic treatment of depression should be made only after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Renal:
Increased plasma concentration of duloxetine occurs in patients with end-stage renal disease (requiring dialysis). Thus, CYMBALTA® is not recommended for patients with end-stage renal disease or severe renal impairment.

Adverse Reactions (see full listing)
CYMBALTA® has been evaluated for safety in 1429 patients with neuropathic pain associated with DPN representing 894.13 patient-years of exposure. Among these 1429 CYMBALTA®-treated patients, 800 patients participated in three 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months (87 patients continued on to an open-label extension phase for an additional 24 weeks). Another 57 patients, originally treated with placebo, were exposed to CYMBALTA® for up to 12 months at 60 mg twice daily in an extension phase. Among these 1429 patients, 881 had ≥6 months of exposure to CYMBALTA®, and 515 had greater than 12 months of exposure.

Approximately 12% of the 800 patients who received CYMBALTA® in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 5% of the 339 patients receiving placebo. Nausea (CYMBALTA® 3.0%, placebo 0.3%), dizziness (CYMBALTA® 1.1%, placebo 0.3%), and somnolence (CYMBALTA® 1.2%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (i.e. discontinuation occurring in at least 1% of the CYMBALTA®-treated patients and at a rate of at least twice that of placebo).

The most commonly observed adverse events in CYMBALTA®-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea, constipation, dry mouth, vomiting, fatigue, decreased appetite, somnolence, erectile dysfunction, and hyperhidrosis.

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Post-market Adverse Drug Reactions

Post-marketing surveillance has identified reports of hepatic injury, including hepatocellular, pure cholestatic and mixed injury ranging from mild elevations in laboratory values to more severe clinical signs and symptoms of liver injury. Isolated cases of liver failure, including fatal cases, have been reported. Most of these cases have been reported in patients with past or current medical and other risk factors for liver injury, including alcohol abuse, hepatitis, or exposure to drugs with known adverse effects on the liver and it is unclear to what extent duloxetine may have played a contributing role.

Adverse events reported rarely (<0.1% and ≥0.01%) include: hematochezia, hallucinations, urinary retention and rash. Hyperglycemia has been reported very rarely (<0.01%) especially in diabetic patients. A causal relationship between CYMBALTA® and the emergence of these events has not been clearly established. (SEE SUPPLEMENTAL PRODUCT INFORMATION)

Drug Interactions:

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2:

CYMBALTA® should not be used concomitantly with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin and enoxacine).

Inhibitors of CYP2D6:

Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average 60%) of duloxetine. Caution is advised if administering CYMBALTA® with inhibitors of CYP2D6 (e.g. SSRIs).

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP2D6:

Caution should be used if duloxetine is co-administered with medications that are predominately metabolized by the CYP2D6 system and which have a narrow therapeutic index such as antiarrhythmics (e.g. flecainide and encainide).

Drugs Metabolized by CYP1A2:

Duloxetine has been shown to be a potential inhibitor of the CYP1A2 isoform in *in vitro* studies. CYMBALTA® is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Drugs Highly Bound to Plasma Protein:

Duloxetine is highly bound to plasma proteins (>90%). Therefore, administration of CYMBALTA® to a patient taking another drug that is highly protein bound may cause increased free concentrations of either drug.

CNS Drugs:

Caution is advised when CYMBALTA® is taken in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. Concomitant use of other drugs with serotonergic activity (e.g. SNRIs, SSRIs, triptans, or tramadol) may result in serotonin syndrome.

Serotonergic Drugs:

Based on the mechanism of action of duloxetine and the potential for serotonin syndrome, caution is advised when CYMBALTA® is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, or St. John's Wort.

Triptans (5HT1 agonists):

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 CYMBALTA® and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Tricyclic Antidepressants (TCA):

Caution is advised in the co-administration of tricyclic antidepressants (TCAs) (e.g. amitriptyline, desipramine, nortriptyline) with duloxetine, because duloxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with duloxetine.

Warfarin:

Increases in INR have been reported when duloxetine was co-administered with warfarin.

Drugs that Affect Gastric Acidity:

CYMBALTA® has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. Caution is advised in using CYMBALTA® in patients with conditions that may slow gastric emptying (e.g. some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine.

To report an adverse effect, please call 1-866-364-4043.

Administration

CYMBALTA® should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

CYMBALTA® is not indicated for use in children less than 18 years of age.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy:

The recommended dose is 60 mg once daily with or without food. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks. Efficacy of CYMBALTA® has been demonstrated within the first week. Some patients may benefit from dosages above the recommended 60 mg once daily up to a maximum dose of 120 mg per day. While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is less well tolerated. Doses above 120 mg have not been evaluated and are not recommended.

As the progression of neuropathic pain associated with DPN is highly variable and management of pain is empirical, the effectiveness of CYMBALTA® must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials, but a one-year open-label safety study was conducted.

Patients with Renal Impairment:

CYMBALTA® is not recommended for patients with end-stage renal disease (requiring dialysis) or with severe renal impairment (estimated creatinine clearance <30 mL/min).

Patients with Hepatic Impairment:

CYMBALTA® should not be used in patients with any liver disease resulting in hepatic impairment.

Elderly Patients:

No dose adjustment is recommended for elderly patients on the basis of age. Caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Treatment of Pregnant Women During the Third Trimester:

When treating pregnant women with CYMBALTA® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering CYMBALTA® in the third trimester.

Discontinuation of Treatment:

When discontinuing CYMBALTA® after more than 1 week of therapy, it is recommended that the dose be tapered to minimize the risk of discontinuation symptoms. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients to or from a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with CYMBALTA®. In addition, at least 5 days should be allowed after stopping CYMBALTA® before starting an MAOI.

Study References

1. Goldstein DJ, Lu Y, Detke MJ, *et al.* Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain* 2005;116:109–118.
2. Cymbalta® Product Monograph. Eli Lilly Canada Inc., October 31, 2007.

Supplemental Product Information

Adverse Reactions:

Treatment-emergent Adverse Events Incidence in the Acute Phase of Neuropathic Pain Associated with DPN Placebo-controlled Trials[1]

System Organ Class/ Adverse Event	Percentage of Patients Reporting Event			
	CYMBALTA® 60 mg QD (N=344)	CYMBALTA® 60 mg BID (N=341)	CYMBALTA® Total* (N=800)	Placebo (N=339)
Gastrointestinal Disorders				
Nausea	24	27	24	9
Diarrhea	11	7	10	7
Constipation	8	12	9	2
Dry mouth	6	10	8	3
Vomiting	5	6	6	3
Dyspepsia[2]	4	4	4	2
***General Disorders and* Administration Site Conditions**				
Fatigue[3]	12	16	12	6
Abdominal pain[4]	5	2	4	2
Infections and Infestations				
Nasopharyngitis	5	7	6	5
Influenza[5]	3	2	3	3
Metabolism and Nutrition Disorders				
Decreased appetite[6]	7	14	10	1
Musculoskeletal and Connective Tissue Disorders				
Back pain	5	2	4	3
Muscle spasm	3	3	3	2

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System Organ Class/ Adverse Event	Percentage of Patients Reporting Event			
	CYMBALTA* 60 mg QD (N=344)	CYMBALTA* 60 mg BID (N=341)	CYMBALTA® Total* (N=800)	Placebo (N=339)
Nervous System Disorder				
Somnolence[7]	17	21	17	5
Headache	12	11	12	9
Dizziness	11	13	11	6
Parathesia[8]	2	2	2	1
Psychiatric Disorders				
Insomnia[9]	8	10	9	5
Agitation[10]	3	3	3	1
Renal and Urinary Disorders				
Poliakiuria	1	3	2	1
Reproductive System and Breast Disorder				
Erectile dysfunction[11]	2	5	3	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[12]	3	4	4	4
Pharyngolaryngeal pain	1	4	3	2
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	10	9	2

* Includes all doses used in DPN studies (i.e. 20 mg QD, 60 mg QD and 60 mg BID)

[1] Events reported by at least 2% of patients treated with CYMBALTA® and more often than placebo. The following events were reported by at least 2% of patients treated with CYMBALTA® for DPNP and had an incidence equal to or less than placebo: pain in extremity, upper respiratory tract infection, arthralgia, cough, influenza, pruritus, musculoskeletal pain (includes myalgia and neck pain), and edema peripheral.

[2] Includes stomach discomfort.

[3] Also includes asthenia.

[4] Includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.

[5] 2.8% of patients treated with CYMBALTA®; 2.7% of patients who received placebo.

[6] Includes anorexia.

[7] Includes hypersomnia, sedation.

[8] Includes hypoasthesia, hypoaesthesia facial, and paraesthesia oral.

[9] Also includes middle insomnia, early morning awakening, and initial insomnia.

[10] Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation.

[11] Male patients only.

[12] 3.9% of patients treated with CYMBALTA®; 3.8% of patients who received placebo.

Other Adverse Events

Weight Changes

In 3 placebo-controlled DPN clinical trials, patients treated with CYMBALTA® for up to 13 weeks experienced a mean weight loss of 0.92 kg, compared with a mean weight gain of 0.16 kg in placebo-treated patients. In long-term trials of up to 52 weeks in duration, the mean decrease in weight was 0.35 kg for CYMBALTA®-treated patients.

Post-market Adverse Drug Reactions

Other adverse reactions reported very rarely (<0.01%) from post-marketing experience include: thrombocytopenia, supraventricular arrhythmia, syndrome of inappropriate antidiuretic hormone (SIADH), glaucoma, gastrointestinal bleeding, hepatitis, jaundice, anaphylactic reaction, hypersensitivity, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, bilirubin increased, hyponatremia, hyperglycemia, muscle spasm, trismus, extrapyramidal disorder, serotonin syndrome, seizures, mania, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, contusion, ecchymosis, erythema multiforme, Stevens-Johnson Syndrome, urticaria, orthostatic hypotension (especially at the initiation of treatment), syncope (especially at initiation of treatment), and hypertensive crisis. A causal relationship between CYMBALTA® and the emergence of these events has not been clearly established.

Management of Overdose

Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, serotonin syndrome, seizures, vomiting, and tachycardia. No specific antidote is known, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, hemoperfusion, and exchange perfusion are unlikely to be beneficial.

Availability

CYMBALTA® (duloxetine hydrochloride) delayed-release capsules are available in 30 mg and 60 mg strengths.

30 mg: The 30 mg capsule has an opaque white body and opaque blue cap, and is imprinted with "30 mg" on the body and "9543" on the cap. It is available in blister cartons of 28 capsules.

60 mg: The 60 mg capsule has an opaque green body and opaque blue cap, and is imprinted with "60 mg" on the body and "9542" on the cap. It is available in blister cartons of 28 capsules.

Complete product monograph available on request:

Eli Lilly Canada Inc.
3650 Danforth Avenue
Toronto, Ontario
M1N 2E8

or visit www.lillyinteractive.ca

"Cymbalta® DELAYED RELEASE CAPSULES
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PrLYRICA® PREGABALIN

PRESCRIBING SUMMARY

PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION: Analgesic Agent

INDICATIONS AND CLINICAL USE

LYRICA is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia in adult patients.

LYRICA may be useful in the management of central neuropathic pain in adult patients for which it has been issued marketing authorization with conditions to reflect the promising nature of the clinical evidence and the need for a confirmatory study to verify its clinical benefit. Patients should be advised of the nature of the authorization.

CONTRAINDICATIONS: Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Tumorigenic Potential: In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Ophthalmological Effects: In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see Product Monograph, **Post-Marketing Adverse Drug Reactions**).

Patients should be informed that if changes in vision occur, they should notify their physician.

Peripheral Edema: In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5508) compared with 2% of patients (42/2,384) in the placebo group. In these studies, 0.5% (28/5508) of pregabalin patients and 0.2% (4/2,384) of placebo patients withdrew due to peripheral edema (see Product Monograph, **ADVERSE REACTIONS, Peripheral Edema**).

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA (pregabalin) and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co administering LYRICA and these agents.

Congestive Heart Failure: In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate (between 0.1% and 1%; see Product Monograph, **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions**).

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see Product Monograph, **ADVERSE REACTIONS, Post-marketing Adverse Drug Reactions**). These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic pain indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Weight Gain: Pregabalin treatment was associated with weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain (see Product Monograph, **ADVERSE REACTIONS, Weight Gain**). Pregabalin-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see Product Monograph, **WARNINGS AND PRECAUTIONS, Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}).

Dizziness and Somnolence: In controlled neuropathic pain studies, pregabalin caused dizziness in 23% of patients (424/1,831) compared to 7% in placebo (58/857). Somnolence was experienced by 14% (256/1,831) and 4% (33/857) of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses.

Abrupt or Rapid Discontinuation: Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see Product Monograph, **ADVERSE REACTIONS, Adverse Events Following Abrupt or Rapid Discontinuation**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions: *Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Peripheral Neuropathic Pain*: The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema, and dry mouth. Adverse events were usually mild to moderate in intensity.

Adverse Events From a Controlled Clinical Study in Central Neuropathic Pain Associated With Spinal Cord Injury: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: somnolence, dizziness, asthenia, dry mouth, edema, myasthenia, constipation, thinking abnormal, amblyopia, and amnesia. Adverse events were usually mild to moderate in intensity.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by telephone: 1-866-234-2345.

ADMINISTRATION

Dosing Considerations

Patients with Impaired Renal Function: **Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in Supplemental Product Information).**

Adults:

Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently.

Central neuropathic pain: The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and

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tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered.

Administration: LYRICA is given orally with or without food.

Supplemental Product Information

Special Populations: ***Geriatrics (≥65 years of age):*** Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see Product Monograph, **WARNINGS AND PRECAUTIONS**, **Geriatrics >65 years of age**).

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labour and Delivery: The effects of pregabalin on labour and delivery in pregnant women are unknown.

Nursing Women: It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended (see Product Monograph, **WARNINGS AND PRECAUTIONS**, **Pediatrics**).

WARNINGS AND PRECAUTIONS: See the Product Monograph for further information on the following: tumorigenic potential, ophthalmological effects, peripheral edema, congestive heart failure, weight gain, dizziness and somnolence, sexual function/reproduction, and special populations.

DRUG INTERACTIONS

Overview: Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Drug Abuse and Dependence/Liability: Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

ADMINISTRATION

Dosage Adjustment Based on Renal Function: Dosing adjustment should be based on creatinine clearance (Cl_{cr}), as indicated in Table 1.

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table below).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (Cl_{cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a] Recommended Dose Escalation*			Dose Regimen
	Starting dose		Maximum daily dose	
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.
* Based on individual patient response and tolerability.
a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
b Supplementary dose is a single additional dose.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans: The highest known dose of pregabalin received in the clinical development program was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin.

Treatment or Management of Overdose: There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Hemodialysis: Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

AVAILABILITY OF DOSAGE FORMS

LYRICA is available in dosage strengths of 25 mg, 50 mg, 75 mg, 100 mg,* 150 mg, 200 mg,* 225 mg,* and 300 mg capsules.

* Not commercially available in Canada

For a copy of the Product Monograph or full Prescribing Information, please contact: Pfizer Canada Medical Information at 1-800-463-6001 or visit www.pfizer.ca.

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AZILECT®

(rasagiline mesylate tablets)

PRESCRIBING SUMMARY

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Antiparkinson Agent

INDICATIONS AND CLINICAL USE

AZILECT (rasagiline mesylate tablets) is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa.

The effectiveness of AZILECT was demonstrated in patients with early Parkinson's disease who were receiving AZILECT as monotherapy and who were not receiving any concomitant dopaminergic therapy. The effectiveness of AZILECT as adjunct therapy was demonstrated in patients with Parkinson's disease who were treated with levodopa.

CONTRAINDICATIONS

Meperidine and Other Analgesics: AZILECT is contraindicated for use with meperidine. Serious reactions have been precipitated with concomitant use of meperidine (e.g., Demerol and other trade names) and MAO inhibitors, including selective MAO-B inhibitors. These reactions have been characterized by coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse and death. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with meperidine.

For similar reasons, AZILECT should not be administered with the analgesic agents tramadol, methadone, and propoxyphene.

Other Drugs: AZILECT should not be used with the antitussive agent dextromethorphan. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. AZILECT is also contraindicated for use with St. John's wort, and cyclobenzaprine (a tricyclic muscle relaxant).

Sympathomimetic Amines: Like other MAOIs, AZILECT is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine and ephedrine). Severe hypertensive reactions have followed the administration of sympathomimetics and non-selective MAO inhibitors. At least one case of hypertensive crisis has been reported in a patient taking the recommended doses of a selective MAO-B inhibitor and a sympathomimetic medication (ephedrine).

Antidepressants: AZILECT should not be administered along with antidepressants. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with a tricyclic, tetracyclic, SSRI, or SNRI antidepressant. Similarly, at least 14 days should elapse after discontinuing treatment with a tricyclic, tetracyclic, SSRI, or SNRI antidepressant before starting AZILECT. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of AZILECT (see WARNINGS).

MAO inhibitors: AZILECT should not be administered along with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with MAO inhibitors.

Surgery: As with other MAOIs, patients taking AZILECT should not undergo elective surgery requiring general anesthesia. Also, they should not be given local anesthesia containing cocaine or sympathomimetic vasoconstrictors. AZILECT should be discontinued at least 14 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, fentanyl, morphine, and codeine may be used cautiously.

Pheochromocytoma: As with other MAOIs, AZILECT is contraindicated in patients with pheochromocytoma.

Safety Information

WARNINGS

Antidepressants: Severe CNS toxicity associated with hyperpyrexia and death has been reported with the combination of tricyclic or tetracyclic antidepressants, non-selective MAOIs (NARDIL, PARNATE), including the reversible MAOI moclobemide, and a selective MAO-B inhibitor, selegiline. These adverse events have included behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, syncope and death.

Serious, sometimes fatal, reactions with signs and symptoms including hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma have been reported in patients receiving a combination of selective serotonin reuptake inhibitors (SSRIs), including fluoxetine (PROZAC), fluvoxamine (LUVOX) sertraline (ZOLOFT), and paroxetine (PAXIL), non-selective MAOIs, including the reversible MAOI moclobemide, or the selective MAO-B inhibitor selegiline. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs).

At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with a tricyclic, tetracyclic, SSRI, or SNRI antidepressant. Similarly, at least 14 days should elapse after discontinuing treatment with a tricyclic, tetracyclic, SSRI, or SNRI antidepressant before starting AZILECT. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of AZILECT (see CONTRAINDICATIONS).

Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations may increase up to 2-fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors (see DOSAGE AND ADMINISTRATION, *Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors*).

Hepatic Insufficiency: AZILECT plasma concentration may increase in patients with mild (up to 2-fold, Child-Pugh score 5-6), moderate (up to 7-fold, Child-Pugh score 7-9), and severe hepatic (Child-Pugh score 10-15) impairment. Patients with mild hepatic impairment should be given the dose of 0.5 mg/day. AZILECT should not be used in patients with moderate or severe hepatic impairment.

PRECAUTIONS

General

Tyramine/rasagiline interaction: Rasagiline should not be used at daily doses exceeding the maximum recommended (1 mg/day) because of the risks associated with nonselective inhibition of MAO. Adequate studies above this dose have not been conducted. Therefore, if rasagiline is to be used without restrictions being placed on diet and concomitant drug use, it is critical to adhere to this maximum dose.

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Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Dyskinesia Due to Levodopa Treatment: When used as an adjunct to levodopa AZILECT may potentiate dopaminergic side effects and exacerbate pre-existing dyskinesia (treatment-emergent dyskinesia occurred in about 18% of patients treated with 0.5 mg or 1 mg rasagiline as an adjunct to levodopa and 10% of patients who received placebo as an adjunct to levodopa). Decreasing the dose of levodopa may ameliorate this side effect.

Postural Hypotension: When used as monotherapy, postural hypotension was reported in approximately 3% of patients treated with 1 mg rasagiline and 5% of patients treated with placebo. In the monotherapy trial, postural hypotension did not lead to drug discontinuation and premature withdrawal in the rasagiline-treated patients or the placebo-treated patients.

When used as an adjunct to levodopa, postural hypotension was reported in approximately 6% of patients treated with 0.5 mg rasagiline, 9% of patients treated with 1 mg rasagiline and 3% of patients treated with placebo. Postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in one (0.7%) patient treated with rasagiline 1 mg/day, no patients treated with rasagiline 0.5 mg/day and no placebo-treated patients.

Clinical trial data suggest that postural hypotension occurs most frequently in the first two months of rasagiline treatment and tends to decrease over time.

Hallucinations: In the monotherapy study, hallucinations were reported as an adverse event in 1.3% of patients treated with 1 mg rasagiline and in 0.7% of patients treated with placebo. In the monotherapy trial, hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 1.3% of the 1 mg rasagiline-treated patients and in none of the placebo-treated patients.

When used as an adjunct to levodopa, hallucinations were reported as an adverse event in approximately 5% of patients treated with 0.5 mg/day, 4% of patients treated with 1 mg/day rasagiline and 3% of patients treated with placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in about 1% of patients treated with 0.5 mg/day or 1 mg/day and none of the placebo-treated patients.

Patients should be cautioned of the possibility of developing hallucinations and instructed to report them to their health care provider promptly should they develop.

Information for Patients

The risk of exceeding the recommended daily dose (1 mg/day) should be explained. The explanation should describe the signs and symptoms associated with MAOI-induced hypertensive reactions. Patients should be urged to immediately report any severe headache or other atypical or unusual symptoms not previously experienced.

Patients should be advised to inform their physician if they are taking, or planning to take, any prescription or over-the-counter drugs, especially with antidepressants and over-the-counter cold medications, since there is a potential for interaction with AZILECT. Patients should not use meperidine with AZILECT.

Patients taking AZILECT as adjunct to levodopa should be advised there is the possibility of increased dyskinesia and postural hypotension.

Patients are advised to monitor for melanomas frequently and on a regular basis. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Patients should be instructed to take AZILECT as prescribed. If a dose is missed the next dose should be taken at the usual time on the following day. The patient should not double up the dose of AZILECT.

Drug Interactions

Meperidine: Serious, sometimes fatal, reactions have been precipitated with concomitant use of meperidine (e.g., Demerol and other trade names) and MAO inhibitors, including selective MAO-B inhibitors (see CONTRAINDICATIONS).

Dextromethorphan: The concomitant use of AZILECT and dextromethorphan was not allowed in clinical studies. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. Therefore, in view of AZILECT's MAO-inhibitory activity, dextromethorphan should not be used concomitantly with AZILECT (see CONTRAINDICATIONS).

Sympathomimetic medications: The concomitant use of AZILECT and sympathomimetic medications was not allowed in clinical studies. Severe hypertensive reactions have followed the administration of sympathomimetics and non-selective MAO inhibitors. One case of hypertensive crisis has been reported in a patient taking the recommended doses of a selective MAO-B inhibitor and a sympathomimetic medication (ephedrine). Therefore, in view of AZILECT's MAO-inhibitory activity, AZILECT should not be used concomitantly with sympathomimetics, including nasal and oral decongestants and cold remedies (see CONTRAINDICATIONS).

MAO inhibitors: AZILECT should not be administered along with other MAO inhibitors, including reversible MAOI (moclobemide) and selective MAO-B inhibitors (selegiline) because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs), tricyclic and tetracyclic antidepressants: Concomitant use of SSRI, tricyclic, and tetracyclic antidepressants with AZILECT is contraindicated (see CONTRAINDICATIONS).

Levodopa/carbidopa: (see PRECAUTIONS, General, *Dyskinesias Due to Levodopa Treatment*).

Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations may increase up to 2-fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors. This could result in increased adverse events (see WARNINGS, *Ciprofloxacin and Other CYP1A2 Inhibitors*).

Theophylline: Co-administration of rasagiline 1 mg/day and theophylline, a substrate of CYP1A2, up to 500 mg twice daily to healthy subjects (n=24), did not affect the pharmacokinetics of either drug.

Laboratory Tests

No specific laboratory tests are necessary for the management of patients on AZILECT.

Use in Pregnancy

Reproductive studies conducted with rasagiline in animals did not reveal any negative effect at doses much higher than those used in the clinical studies. However, there are no adequate and well-controlled studies of rasagiline in pregnant women. Because animal reproduction studies are not always predictive of human response, AZILECT should be used during pregnancy only if clearly needed.

Nursing Mothers

Experimental data indicated that rasagiline inhibits prolactin secretion and, thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AZILECT is administered to a nursing woman.

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Use in Children

The safety and effectiveness of AZILECT in patients below 18 years of age have not been established.

Use in the Elderly

Approximately half of patients in clinical trials were 65 years and over. There were no significant differences in the safety profile of the geriatric and non-geriatric patients.

Renal Insufficiency: Conclusive data are not available for renally-impaired patients. As unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment. Due to the absence of adequate safety data, rasagiline should not be administered to patients with moderate to severe renal impairment.

ADVERSE REACTIONS

During the clinical development of AZILECT (rasagiline mesylate tablets), 1361 Parkinson's disease patients received AZILECT as initial monotherapy, or as adjunct therapy to levodopa. As these two populations differ, not only in the adjunct use of levodopa during AZILECT treatment, but also in the severity and duration of their disease, they may have differential risks for various adverse events. Therefore, most of the adverse events data in this section are presented separately for each population.

Monotherapy

Adverse events leading to discontinuation in controlled clinical studies:

In the double-blind, placebo-controlled trials conducted in patients receiving AZILECT as monotherapy, approximately 5% of the 149 patients treated with rasagiline discontinued treatment due to adverse events compared to 2% of the 151 patients who received placebo.

The only adverse event that led to the discontinuation of more than one patient was hallucinations.

Adverse event incidence in controlled clinical studies:

The most commonly observed adverse events that occurred in ≥5% of patients receiving AZILECT 1 mg as monotherapy (n=149) participating in the double-blind, placebo-controlled trial and that were at least 1.5 times the incidence in the placebo group (n=151), were: flu syndrome, arthralgia, depression, dyspepsia and fall.

Adjunct therapy

Adverse events leading to discontinuation in controlled clinical studies:

In a double-blind, placebo-controlled trial (PRESTO) conducted in patients treated with AZILECT as adjunct to levodopa therapy, approximately 9% of the 164 patients treated with AZILECT 0.5 mg/day and 7% of the 149 patients treated with AZILECT 1 mg/day discontinued treatment due to adverse events compared to 6% of the 159 patients who received placebo. The AEs that led to discontinuation of more than one rasagiline-treated patient were diarrhea, weight loss, hallucination, and rash. Adverse event reporting was considered more reliable for PRESTO than for the second controlled trial (LARGO); therefore only the adverse event data from PRESTO are presented in this section of labelling.

Adverse event incidence in controlled clinical studies:

The most commonly observed adverse events that occurred in ≥5% of patients receiving AZILECT 1 mg (n=149) as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (PRESTO) and that were at least 1.5 times the incidence in the placebo group (n=159) in descending order of difference in incidence were dyskinesia, accidental injury, weight loss, postural hypotension, vomiting, anorexia, arthralgia, abdominal pain, nausea, constipation, dry mouth, rash, ecchymosis, somnolence and paresthesia.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345

Toll-free fax: 1-866-678-6789

By email: cadrmp@hc-sc.gc.ca

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations:

The recommended and maximum dose in both monotherapy and adjunct therapy is 1 mg once daily.

AZILECT can be taken with or without food.

There is no evidence that additional benefit will be obtained from the administration of doses higher than that recommended. Furthermore, higher doses will likely result in a loss of selectivity of rasagiline towards MAO-B with an increase in the inhibition of MAO-A. There is an increased risk of adverse reactions with higher doses as well as an increased risk of hypertensive episode ("cheese reaction").

Monotherapy

The recommended AZILECT dose for the treatment of Parkinson's disease patients is 1 mg administered once daily.

Adjunctive Therapy

The dosage of AZILECT shown to be effective in controlled clinical trials for adjunct therapy was 0.5 – 1 mg once daily. The recommended initial dose is 0.5 mg administered once daily. If a sufficient clinical response is not achieved, the dose may be increased to 1 mg administered once daily.

Change of levodopa dose in adjunct therapy: When AZILECT is used in combination with levodopa a reduction of the levodopa dosage may be considered based upon individual response. During the controlled trials of AZILECT as adjunct therapy to levodopa, levodopa dosage was reduced in some patients. In clinical studies, dosage reduction of levodopa was allowed within the first 6 weeks if dopaminergic side effects, including dyskinesia and hallucinations, emerged. In the PRESTO study levodopa dosage reduction occurred in 8% of patients in the placebo group and in 16% and 17% of patients in the 0.5 mg/day and 1 mg/day rasagiline groups, respectively. In those patients who had levodopa dosage reduced, the dose was reduced on average by about 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In the LARGO study levodopa dosage reduction occurred in 6% of patients in the placebo group and in 9% in the rasagiline 1 mg/day group. In patients who had their levodopa dosage reduced, the dose was reduced on average by about 13% and 11% in the placebo and the rasagiline groups, respectively.

Patients with Hepatic Impairment: AZILECT plasma concentration will increase in patients with hepatic impairment. Patients with mild hepatic impairment should use AZILECT 0.5 mg daily of AZILECT. AZILECT should not be used in patients with moderate to severe hepatic impairment (see WARNINGS, *Hepatic Insufficiency).*

Patients with Renal Impairment: Conclusive data are not available for renally-impaired patients. As unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment. Due to the absence of adequate safety data, rasagiline should not be administered to patients with moderate to severe renal impairment.

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Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors: Rasagiline plasma concentrations are expected to double in patients taking concomitant ciprofloxacin and other CYP1A2 inhibitors. Therefore, patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should use 0.5 mg daily of AZILECT (see WARNINGS, *Ciprofloxacin and Other CYP1A2 Inhibitors).*

Study References

1. TEVA Neuroscience. AZILECT® Product Monograph. May 2008.

Supplemental Product Information

ADVERSE REACTIONS

Monotherapy

Table 1 lists treatment-emergent adverse events that occurred in ≥2% of patients receiving AZILECT as monotherapy participating in the double-blind, placebo-controlled trial and were numerically more frequent than in the placebo group.

Table 1. Treatment-Emergent* Adverse Events in AZILECT 1 mg-Treated Monotherapy Patients

Placebo-Controlled Studies Without Levodopa Treatment	AZILECT 1 mg (n=149) % of patients	Placebo (n=151) % of patients
Headache	14	12
Arthralgia	7	4
Dyspepsia	7	4
Depression	5	2
Fall	5	3
Flu syndrome	5	1
Conjunctivitis	3	1
Fever	3	1
Gastroenteritis	3	1
Rhinitis	3	1
Arthritis	2	1
Ecchymosis	2	0
Malaise	2	0
Neck Pain	2	0
Paresthesia	2	1
Vertigo	2	1

*Incidence ≥2% in AZILECT 1 mg group and numerically more frequent than in placebo group.

Other events of potential clinical importance reported by 1% or more of Parkinson's disease patients receiving AZILECT as monotherapy, and at least as frequent as in the placebo group, in descending order of frequency, include: dizziness, diarrhea, chest pain, albuminuria, allergic reaction, alopecia, angina pectoris, anorexia, asthma, hallucinations, impotence, leukopenia, libido decreased, liver function tests abnormal, skin carcinoma, syncope, vesiculobullous rash, vomiting.

There were no significant differences in the safety profile based on age or gender.

Adjunct therapy

Table 2 lists treatment-emergent adverse events that occurred in ≥2% of patients treated with AZILECT 1 mg/day as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (PRESTO) and that were numerically more frequent than the placebo group. The table also shows the rates for the 0.5 mg group in PRESTO.

Table 2. Incidence of Treatment-Emergent* Adverse Events in Patients Receiving AZILECT as Adjunct to Levodopa Therapy in PRESTO

	AZILECT 1 mg + Levodopa (n=149) % of patients	AZILECT 0.5 mg + Levodopa (n=164) % of patients	Placebo + Levodopa (n=159) % of patients
Dyskinesia	18	18	10
Accidental injury	12	8	5
Nausea	12	10	8
Headache	11	8	10
Fall	11	12	8
Weight loss	9	2	3
Constipation	9	4	5
Postural hypotension	9	6	3
Arthralgia	8	6	4
Vomiting	7	4	1
Dry mouth	6	2	3
Rash	6	3	3
Somnolence	6	4	4
Abdominal pain	5	2	1
Anorexia	5	2	1
Diarrhea	5	7	4
Ecchymosis	5	2	3
Dyspepsia	5	4	4
Paresthesia	5	2	3
Abnormal dreams	4	1	1
Hallucinations	4	5	3
Ataxia	3	6	1
Dyspnea	3	5	2
Infection	3	2	2
Neck pain	3	1	1
Sweating	3	2	1
Tenosynovitis	3	1	0
Dystonia	3	2	1
Gingivitis	2	1	1
Hemorrhage	2	1	1
Hernia	2	1	1
Myasthenia	2	2	1

*Incidence ≥2% in AZILECT 1 mg group and numerically more frequent than in placebo group.

Several of the more common adverse events seemed dose-related, including weight loss, postural hypotension, and dry mouth.

Other events of potential clinical importance reported in PRESTO by 1% or more of patients treated with rasagiline 1 mg/day as adjunct to levodopa therapy and at least as frequent as in the placebo group, in descending order of frequency, include: skin carcinoma, anemia, albuminuria, amnesia, arthritis, bursitis, cerebrovascular accident, confusion, dysphagia, epistaxis, leg cramps, pruritus, skin ulcer.

There were no significant differences in the safety profile based on age or gender.

Other Adverse Events Observed During All Phase II/III Clinical Trials

Rasagiline was administered to approximately 1361 patients during all PD phase II/III clinical trials. About 771 patients received rasagiline for at least one year, approximately 361 patients received rasagiline for at least two years and 245 patients received rasagiline for more than three years, with 138 patients treated for more than five years. The long-term safety profile was similar to that observed with shorter duration exposure.

The frequencies listed below represent the proportion of the 1361 individuals exposed to rasagiline who experienced events of the type cited.

All events that occurred at least twice (or once for serious or potentially serious events) except those already listed above, trivial events, terms too vague to be meaningful, adverse events with no plausible relation to treatment and events that would be expected in patients of the age studied were reported without regard to determination of a causal relationship to rasagiline.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients, infrequent adverse events are defined as those occurring in less than 1/100 to at least 1/1000 patients and rare adverse events are defined as those occurring in fewer than 1/1000 patients.

Body as a whole: *Frequent:* asthenia; *Infrequent:* chills, face edema, flank pain, photosensitivity reaction.

Cardiovascular system: *Frequent:* bundle branch block; *Infrequent:* deep thrombophlebitis, heart failure, migraine, myocardial infarct, phlebitis, ventricular tachycardia; *Rare:* arterial thrombosis, atrial arrhythmia, AV block complete, AV block second degree, bigeminy, cerebral hemorrhage, cerebral ischemia, ventricular fibrillation.

Digestive system: *Frequent:* gastrointestinal hemorrhage; *Infrequent:* colitis, esophageal ulcer, esophagitis, fecal incontinence, intestinal obstruction, mouth ulceration, stomach ulcer, stomatitis, tongue edema; *Rare:* hematemesis, hemorrhagic gastritis, intestinal perforation, intestinal stenosis, jaundice, large intestine perforation, megacolon, melena.

Hemic and Lymphatic systems: *Infrequent:* macrocytic anemia; *Rare:* purpura, thrombocythemia.

Metabolic and Nutritional disorders: *Infrequent:* hypocalcemia.

Musculoskeletal system: *Infrequent:* bone necrosis, muscle atrophy; *Rare:* arthrosis.

Nervous system: *Frequent:* abnormal gait, anxiety, hyperkinesia, hypertonia, neuropathy, tremor; *Infrequent:* agitation, aphasia, circumoral paresthesia, convulsion, delusions, dementia, dysarthria, dysautonomia, dysesthesia, emotional lability, facial paralysis, foot drop, hemiplegia, hypesthesia, incoordination, manic reaction, myoclonus, neuritis, neurosis, paranoid reaction, personality disorder, psychosis, wrist drop; *Rare:* apathy, delirium, hostility, manic depressive reaction, myelitis, neuralgia, psychotic depression, stupor.

Respiratory system: *Frequent:* cough increased; *Infrequent:* apnea, emphysema, laryngismus, pleural effusion, pneumothorax; *Rare:* interstitial pneumonia, larynx edema, lung fibrosis.

Skin and Appendages: *Infrequent:* eczema, urticaria; *Rare:* exfoliative dermatitis, leukoderma.

Special senses: *Infrequent:* blepharitis, deafness, diplopia, eye hemorrhage, eye pain, glaucoma, keratitis, ptosis, retinal degeneration, taste perversion, visual field defect; *Rare:* blindness, parosmia, photophobia, retinal detachment, retinal hemorrhage, strabismus, taste loss, vestibular disorder.

Urogenital system: *Frequent:* hematuria, urinary incontinence; *Infrequent:* acute kidney failure, dysmenorrhea, dysuria, kidney calculus, nocturia, polyuria, scrotal edema, sexual function abnormal, urinary retention, urination impaired, vaginal hemorrhage, vaginal moniliasis, vaginitis; *Rare:* abnormal ejaculation, amenorrhea, anuria, epididymitis, gynecomastia, hydroureter, leukorrhea, priapism.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No cases of AZILECT (rasagiline mesylate tablets) overdose were reported in clinical trials.

Rasagiline was well tolerated in a single-dose study in healthy volunteers receiving 20 mg/day and in a ten-day study in healthy volunteers receiving 10 mg/day. Adverse events were mild or moderate. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg of rasagiline there were three reports of cardiovascular side effects (including hypertension and postural hypotension) which resolved following treatment discontinuation.

Symptoms of overdosage, although never observed with rasagiline during clinical development, may resemble those observed with non-selective MAO inhibitors.

Although no cases of overdose have been observed with rasagiline, the following description of presenting symptoms and clinical course is based upon overdose descriptions of non-selective MAO inhibitors.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

There is no specific antidote for rasagiline overdose. The following suggestions are offered based upon the assumption that rasagiline overdose may be modeled after non-selective MAO inhibitor poisoning. Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

A poison control centre should be called for the most current treatment guidelines.

Based on product monograph dated May 14, 2008.

Product Monograph available on request.

℞ AZILECT®
(rasagiline mesylate tablets)

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Montreal, Quebec H3A 3L4

See our AD on page A-6

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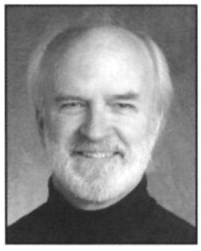
CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

The Canadian Neurological Sciences Federation (CNSF) and Neurological Sciences Foundation of Canada (NSFC)

2008 – 2009 Board of Directors and Committee Chairs



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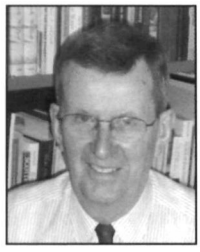

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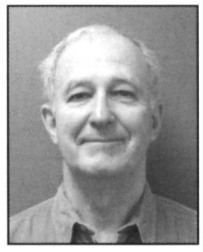

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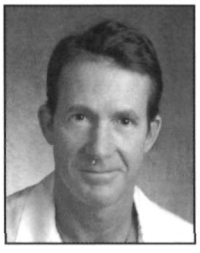

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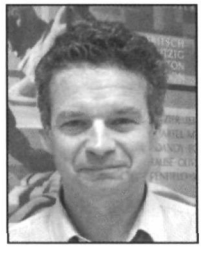

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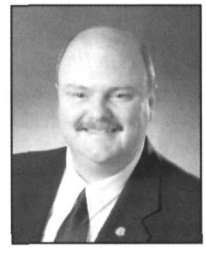

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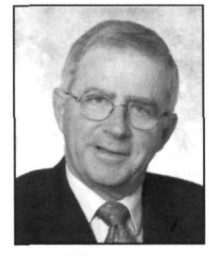

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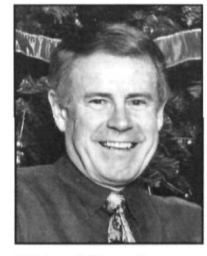

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Canadian Neurological Sciences Federation
44th Annual Congress

Preliminary Program
as at April 16, 2009.

CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

Tuesday, June 9/09

7:15 – 8:30	Residents' Breakfast
8:30 - 5:00	ALS
8:15 - 5:00	Advances in the Neurobiology of Disease ***Chairs: Peter Dirks and Peter Smith***
8:30 - 5:00	Child Neurology Day ***Chairs: Harvey Sarnat and Joe Dooley***
12:00 - 1:30	Lunch
6:00 - 8:00	Epilepsy Video Session ***Chair: Richard McLachlan***
6:00 - 8:00	Movement Disorders SIG ***Chair: Alex Rajput***
6:00 - 8:00	Headache SIG ***Chair: Jonathan Gladstone***
6:00 - 8:00	Neuromuscular SIG ***Chair: Kristine Chapman***

Wednesday, June 10/09

8:00 - 10:00	Grand Opening Plenary-Scientific & Technical Advances in the Clinical Neurosciences: ***Cornelius Tulleken (ELANA)/ Mark Bernstein (Ethics) / Ivar Mendez – Richardson***
10:00 - 10:15	Coffee Break
10:15 - 11:45	Chair's Select Plenary Presentations
11:45 - 12:00	Clinical Trial Announcements
12:00 - 1:30	Epilepsy Co-developed Industry Symposium (UCB Pharma Canada)
12:00 - 1:30	Neuropathic Pain Co-developed Industry Symposium (Pfizer Canada)
1:30 - 5:00	Concurrent Neurovascular Course - Neuroradiology ***Chair: Timo Krings***
1:30 - 5:00	Concurrent Neurovascular Course – Clinical Neurovascular ***Chairs: M. Findlay & G. Gubitz***
1:30 - 5:00	Spine ***Chair: Eric Massicotte***
1:30 - 5:00	Neurocritical Care ***Chair: Joanne Teitelbaum***

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Rapid, reliable relief. ℞ **RELPAX**®
eletriptan HBr 40 mg

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Migraine Therapy

INDICATIONS AND CLINICAL USE

RELPAX (eletriptan hydrobromide) is indicated for the acute treatment of migraine with or without aura in adults.

RELPAX tablets are 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 **RELPAX** tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

RELPAX tablets are 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 eletriptan. 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 RELPAX may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS AND PRECAUTIONS).

Eletriptan is metabolized by the CYP3A4 enzyme. Therefore, RELPAX is contraindicated within 72 h of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. RELPAX is contraindicated within 72 h with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections of their labeling (see DRUG INTERACTIONS and ADMINISTRATION).

RELPAX is contraindicated within 24 h of treatment with another 5-HT$_1$ agonist, an ergotamine-containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide.

RELPAX is also contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine; in patients with severe hepatic impairment; and in patients with known hypersensitivity to eletriptan or any of its inactive ingredients.

SPECIAL POPULATIONS

Pregnant women

The safety of eletriptan in pregnant women has not been established. Administration of **RELPAX** tablets should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus (see **Supplemental Product Information**).

Nursing women

Caution should be exercised when **RELPAX** tablets are administered to nursing women. Eletriptan is excreted in human breast milk (see **Supplemental Product Information**).

Pediatrics (<18 years of age)

Safety and effectiveness of **RELPAX** tablets in pediatric patients have not been established; therefore, **RELPAX** is not recommended for use in patients under 18 years of age.

The efficacy of **RELPAX** tablets (40 mg) in patients 11-17 was not established in a randomized, placebo-controlled trial of 274 adolescent migraineurs.

Geriatrics (>65 years of age)

RELPAX has been given to only 50 patients over the age of 65. Blood pressure was increased to a greater extent in elderly subjects than in young subjects. Experience of the use of **RELPAX** in patients aged >65 years is limited. Therefore, the use of **RELPAX** in patients over 65 years is not recommended (see **Supplemental Product Information**).

Safety Information

WARNINGS AND PRECAUTIONS

General

RELPAX tablets should only be used where a clear diagnosis of migraine has been established.

CYP3A4 inhibitors

See CONTRAINDICATIONS above.

Cardiovascular

Risk of myocardial ischemia and/or infarction and other cardiac events: As with other triptans, eletriptan has been associated with transient pain or pressure sensation in the chest or throat. Because of the potential of 5-HT$_1$ agonists to cause coronary vasospasm, eletriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that eletriptan not be given to patients in whom unrecognized 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 >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 modest, at best. 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, eletriptan 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 1st dose of eletriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received eletriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining, on the 1st occasion of use, an electrocardiogram (ECG) during the interval immediately following administration of eletriptan, in 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.

It is recommended that patients who are intermittent long-term users of 5-HT$_1$ agonists including eletriptan, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use eletriptan.

If symptoms consistent with angina occur after the use of eletriptan, 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 therapy with eletriptan.

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness, and tightness) has been reported after administration of eletriptan. Because 5-HT$_1$ agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following eletriptan should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following eletriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, Clinical trial adverse drug reactions).

Cardiac events and fatalities associated with 5-HT$_1$ agonists: As with other triptans, eletriptan may cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT$_1$ agonists. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low.

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

As with other 5-HT$_1$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with **RELPAX** tablets in the precordium, throat and jaw. Events that are localized to the chest, throat, neck and jaw have not been associated with arrhythmias or ischemic ECG changes in clinical trials.

Because 5-HT$_1$ agonists 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

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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 the use of any 5-HT_1 agonist are candidates for further evaluation (see **CONTRAINDICATIONS** and **Supplemental Product Information**).

Cerebrovascular events and fatalities associated with 5-HT_1 agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Increase in blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving other 5-HT_1 agonists with and without a history of hypertension. In clinical pharmacology studies, oral eletriptan (at doses of 60 mg or more) was shown to cause small transient dose-related increases in blood pressure, predominantly diastolic, consistent with its mechanism of action and with other 5-$HT_{1B/1D}$ agonists. The effect was more pronounced in renally impaired and elderly subjects. A single patient with hepatic cirrhosis received eletriptan 80 mg and experienced a blood pressure of 220/96 mmHg 5 h after dosing. The treatment-related event persisted for 7 h.

RELPAX tablets are contraindicated in patients with uncontrolled or severe hypertension (see **CONTRAINDICATIONS**).

Hepatic

The effects of severe hepatic impairment on eletriptan metabolism were not evaluated. **RELPAX** tablets should not be given to patients with severe hepatic impairment.

No dose adjustment is necessary in mild to moderate impairment (see **ADMINISTRATION** and **Supplemental Product Information**).

Neurologic

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic 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 1st dose of eletriptan.

Seizures: Caution should be observed if eletriptan is to be used in patients with a history of seizures or other risk factors, such as structural brain lesions, which lower the convulsion threshold.

Psychomotor effect

Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that **RELPAX** does not affect them adversely.

Renal

There was no significant change in clearance observed in subjects with mild, moderate or severe renal impairment. In some of these patients, an elevation in blood pressure was observed (see **ADMINISTRATION**).

Sensitivity/resistance

Hypersensitivity: Owing to the possibility of cross-reactive hypersensitivity reactions, **RELPAX** should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists (see **ADVERSE REACTIONS** and **Supplemental Product Information**).

ADVERSE REACTIONS

Adverse drug reaction overview

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

Typical 5-HT_1 agonist adverse reactions

As with other 5-HT_1 agonists, **RELPAX** 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.

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. **RELPAX** is contraindicated in patients with uncontrolled hypertension (see **CONTRAINDICATIONS**).

Clinical trial adverse drug reactions

Among 5,984 patients who treated a single migraine headache with **RELPAX** 20, 40 or 80 mg tablets in short-term, placebo-controlled trials, the most common and dose-related adverse events (AEs) reported with treatment with **RELPAX** were asthenia (7.2%), nausea (7.8%), dizziness (5.7%) and somnolence (5.2%) (see **Supplemental Product Information** and Table 1 below).

RELPAX tablets are generally well tolerated. Across all doses, most AEs were mild and transient. The frequency of AEs in clinical trials did not increase when up to 2 doses of **RELPAX** tablets were taken within 24 h. The incidence of AEs in controlled clinical trials was not affected by gender, age, or race of patients. AE frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis, (e.g., SSRIs, beta-blockers, calcium channel blockers, tricyclic antidepressants), estrogen replacement therapy and oral contraceptives.

DRUG INTERACTIONS

Effects of other drugs on eletriptan

CYP3A4 inhibitors: See **CONTRAINDICATIONS** and **Supplemental Product Information**.

Ergot-containing drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine [DHE] or methysergide) and **RELPAX** tablets within 24 h is not recommended (see **CONTRAINDICATIONS**).

Other 5-HT_1 agonists: See **CONTRAINDICATIONS**.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when co-administered with 5-HT_1 agonists. If concomitant treatment with eletriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug-food interactions

The AUC and C_{max} of eletriptan are increased by approximately 20 to 30% following oral administration with a high fat meal.

Health Canada may be notified by phone of serious or unexpected reaction to this drug at: 1-866-234-2345.

Administration

Dosing considerations

RELPAX tablets should be taken as early as possible after the onset of a migraine attack, but are also effective if taken at a later stage. **RELPAX** tablets should not be used prophylactically.

Recommended dose and dosage adjustment

Adult (18-65 years of age): In controlled clinical trials, single doses of 20 mg and 40 mg were effective for the acute treatment of migraine in adults. A greater proportion of patients had a response following a 40 mg dose than following a 20 mg dose. Individuals may vary in response to doses of **RELPAX** tablets.

When initiating treatment with **RELPAX**, a starting dose of 20 mg or 40 mg may be considered. Patients who do not obtain satisfactory efficacy after an initial trial of 20 mg may be effectively treated with 40 mg in subsequent migraine attacks. The choice of dose should therefore be made on an individual basis, according to the clinical status of the patient and weighing the possible risk/benefit of the 40 mg dose. A minimal effective dose should be used.

If after an initial dose of 20 mg, headache improves but then returns, a repeat dose of 20 mg may be beneficial and should be taken at least 2 h after the initial dose. If an initial dose of 40 mg is taken, a 2nd dose is not recommended.

If the initial dose is ineffective, controlled clinical trials have not shown a benefit of a 2nd dose to treat the same attack.

The maximum daily dose should not exceed 40 mg.

The safety of treating an average of more than 3 headaches in a 30-day period has not been established.

Patients receiving potent CYP3A4 inhibitors

Eletriptan is metabolized by the CYP3A4 enzyme. Concomitant use of **RELPAX** and potent CYP3A4 inhibitors may lead to significant increases in AUC and C_{max}, therefore **RELPAX** tablets are contraindicated within 72 h of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, clarithromycin, troleandomycin, ritonavir, nelfinavir and nefazodone. **RELPAX** is contraindicated within 72 h with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the **CONTRAINDICATIONS** or **WARNINGS AND PRECAUTIONS** sections of their labeling (see **DRUG INTERACTIONS** and **CONTRAINDICATIONS**).

Patients with hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. As **RELPAX** has not been studied in patients with severe hepatic impairment, it is contraindicated in these patients (see **CONTRAINDICATIONS**).

Patients with renal impairment

In some patients with renal impairment, an elevation in blood pressure was observed. A total daily dose of greater than 20 mg should be administered with caution (see **WARNINGS AND PRECAUTIONS**).

Administration

RELPAX tablets should be swallowed whole with water.

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Study References

1. RELPAX Product Monograph, Pfizer Canada Inc., March 2006.
2. Sheftell F *et al.* Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache* 2003;43:202-213.
3. Mathew NT *et al.* Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache* 2003;43:214-222.
4. Sandrini G *et al.*: Eletriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. *Neurology* 2002;59:1210-1217.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Pregnant women

In reproductive toxicity studies in rats and rabbits, oral administration of eletriptan was associated with developmental toxicity (decreased fetal and pup weights) and an increased incidence of fetal structural abnormalities. Effects on fetal and pup weights were observed at doses that were, on a mg/m^2 basis, 6 to 12 times greater than the clinical maximum recommended daily dose (MRDD) of 80 mg. The increase in structural alterations occurred in the rat and rabbit at doses that, on a mg/m^2 basis, were 12 times greater than (rat) and approximately equal to (rabbit) the MRDD.

When pregnant rats were administered eletriptan during the period of organogenesis at doses of 10, 30 or 100 mg/kg/d, fetal weights were decreased and the incidences of vertebral and sternebral variations were increased at 100 mg/kg/d (approximately 12 times the MRDD on a mg/m^2 basis). The 100 mg/kg dose was also maternally toxic, as evidenced by decreased maternal body weight gain during gestation. The no-effect dose for developmental toxicity in rats exposed during organogenesis was 30 mg/kg, which is approximately 4 times the MRDD on a mg/m^2 basis.

When doses of 5, 10 or 50 mg/kg/d were given to New Zealand White rabbits throughout organogenesis, fetal weights were decreased at 50 mg/kg, which is approximately 12 times the MRDD on a mg/m^2 basis. The incidences of fused sternebrae and vena cava deviations were increased in all treated groups. Maternal toxicity was not produced at any dose. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established, and the 5 mg/kg dose is approximately equal to the MRDD on a mg/m^2 basis.

When female rats were treated with 5, 15 or 50 mg/kg/d during late gestation and lactation, *in utero* deaths were increased and pup weights were decreased postnatally at 50 mg/kg/d. The effect on pup weights persisted to adulthood. Exposure to parent drug (AUC) at that dose was approximately 4 times that achieved in humans receiving the MRDD. The 50 mg/kg/d dose was mildly maternally toxic, as evidenced by minimally decreased maternal body weight gain during gestation. The no-effect dose for developmental effects was 15 mg/kg, a dose that produced an AUC for parent drug approximately equal to that achieved in humans receiving the MRDD.

Nursing women

In 1 study of 8 women given a single dose of 80 mg, the mean total amount of eletriptan in breast milk over 24 h in this group was approximately 0.02% of the administered dose. The ratio of eletriptan mean concentration in breast milk to plasma was 1:4, but there was great variability. The resulting eletriptan concentration-time profile was similar to that seen in the plasma over 24 h, with very low concentrations of drug (mean 1.7 ng/mL) still present in the milk 18-24 h postdose. The N-desmethyl active metabolite was not measured in the breast milk.

Geriatrics (>65 years of age)

The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults. There is a statistically significant increase in half-life (from about 4.4 h to 5.7 h) between elderly (65 to 93 years of age) and younger adult subjects (18 to 45 years of age).

Cardiovascular

Cardiac events and fatalities associated with 5-HT$_1$ agonists:

Pre-marketing experience with eletriptan: In a clinical pharmacology study, in subjects undergoing diagnostic coronary angiography, a subject with a history of angina, hypertension and hypercholesterolemia, receiving intravenous eletriptan (C_{max} of 127 ng/mL equivalent to 60 mg oral eletriptan), reported chest tightness and experienced angiographically documented coronary vasospasm with no ECG changes indicative of ischemia. There was also 1 report of atrial fibrillation in a patient with a past history of atrial fibrillation.

In another coronary angiography study, supratherapeutic doses of eletriptan (comparable to 2 X 80 mg in the presence of a potent CYP3A4 inhibitor), administered as a rapid intravenous infusion, were compared with a standard formulation and dose of sumatriptan (6mg sc) and placebo. There were 8 subjective reports of vasoconstriction in the eletriptan group (compared with no cases in the sumatriptan or placebo groups); however, mean change in coronary artery diameter, as determined by quantitative coronary angiography, did not differ in the 3 treatment groups.

Post-marketing experience with eletriptan: Cases of myocardial infarction and cardiac death have been reported in patients with cardiovascular risk factors (e.g., hypertension, hyperlipidemia, strong family history of CAD) or with inappropriate concomitant use of therapeutic doses of eletriptan and other triptans.

The uncontrolled nature of post-marketing surveillance, however, makes it impossible to determine definitively if the cases were actually caused by eletriptan or to reliably assess causation in individual cases.

Special cardiovascular pharmacology studies with another 5-HT$_1$ agonist: In subjects (n=10) with suspected CAD 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 4 subjects. Clinically significant increases in blood pressure were experienced by 3 of the subjects (2 of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant CAD.

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.

Other vasospasm-related events: 5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery spasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain, and bloody diarrhea have been reported with 5-HT$_1$ agonists.

Dependence/tolerance

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

Hepatic

Subjects with mild or moderate hepatic impairments demonstrated an increase in AUC (34%), C_{max} (18%) and in half-life.

Ophthalmologic

Corneal opacities: Transient corneal opacities were seen in dogs receiving oral eletriptan at ≥5 mg/kg. They were observed during the 1st week of treatment, but were not present thereafter despite continued treatment. Exposure at the no-effect dose level of 2.5 mg/kg exceeded that achieved in humans at the MRDD.

Preclinical toxicology

Binding to melanin-containing tissues: In rats treated with a single intravenous (3 mg/kg) dose of radiolabelled eletriptan, elimination of radioactivity from the retina was prolonged, suggesting that eletriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin-rich tissues over time, this raises the possibility that eletriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with eletriptan in the 1-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.

Carcinogenicity: Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by administering eletriptan in the diet at doses of up to 400 mg/kg/d. In rats, the incidence of testicular interstitial cell adenomas was increased at the high dose of 75 mg/kg/d. The estimated exposure (AUC) to parent drug at that dose was approximately 6 times that achieved in humans receiving the MRDD of 80 mg, and at the no-effect dose of 15 mg/kg/d it was approximately 2 times the human exposure at the MRDD. In mice, the incidence of hepatocellular adenomas was increased at the high dose of 400 mg/kg/d. The exposure to parent drug (AUC) at that dose was approximately 18 times that achieved in humans receiving the MRDD, and the AUC at the no-effect dose of 90 mg/kg/d was approximately 7 times the human exposure at the MRDD.

Mutagenicity: Eletriptan was not mutagenic in bacterial or mammalian cell assays *in vitro*, testing negative in the Ames reverse mutation test and the hypoxanthineguanine phosphoribosyl transferase (HGPRT) mutation test in Chinese hamster ovary cells. It was not clastogenic in 2 *in vivo* mouse micronucleus assays. Results were equivocal in *in vitro* human lymphocyte clastogenicity tests, in which the incidence of polyploidy was increased in the absence of metabolic activation (-S9 conditions), but not in the presence of metabolic activation.

Sensitivity/resistance

Hypersensitivity: 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 (see **ADVERSE REACTIONS**).

Sexual function/reproduction

Impairment of fertility: In a rat fertility and early embryonic development study, doses tested were 50, 100 and 200 mg/kg/d, resulting in systemic exposures to parent drug in rats, based on AUC, that were 4, 8, and 16 times MRDD, respectively, in males and 7, 14, and 28 times MRDD, respectively, in females. There was a prolongation of the estrous cycle at the 200 mg/kg/d dose due to an increase in duration of estrus, based on vaginal smears. There were also dose-related, statistically significant decreases in mean numbers of corpora lutea per dam at all 3 doses, resulting in decreases in mean numbers of implants and viable fetuses per dam. This suggests a partial inhibition of ovulation by eletriptan. There was no effect on fertility of males and no other effect on fertility of females.

ADVERSE REACTIONS

Clinical trial adverse drug reactions

In the clinical program, 7,483 subjects have received **RELPAX** tablets and 1,595 have received placebo.

In Phase 2/3 clinical trials for the treatment of migraine, safety data were obtained for 6,954 subjects treated with eletriptan and 1,376 subjects treated with placebo. In the clinical pharmacology program, 529 subjects received eletriptan and 219 received placebo.

Table 1 lists the most common AEs that occurred in the subset of 7,131 patients with migraine who received eletriptan doses of 20 mg, 40 mg, 80 mg or placebo in worldwide, placebo-controlled clinical trials. AEs that were more frequent in a **RELPAX** treatment group compared to the placebo group with an incidence >1% are included in Table 1. 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, those frequency estimates may not apply, as the conditions of use, reporting behaviour, and the kinds of patients treated may differ.

Table 1. Treatment-emergent adverse events by initial oral dose of RELPAX and placebo reported by ≥1% patients with migraine from controlled clinical trials

	Placebo	20 mg	40 mg	80 mg
Number of patients	1559	536	2951	2085
Symptoms of potentially cardiac origin				
Chest sensations*	1.1	0.4	2.2	4.4
Neck/throat/jaw sensations*	0.2	0.2	1.4	2.2
Palpitations	0.9	0.7	1.3	1.8
Upper limb sensations*	0.1	0.2	0.6	1.1
Neurological				
Dizziness	2.8	2.4	5.1	7.2
Drowsiness	2.8	1.9	4.9	5.9
Head/face sensations*	0.7	1.5	1.2	1.8
Headache	2.4	2.8	2.8	3.5
Hypertonia	0.2	0.9	0.6	1.8
Vertigo	0.5	0.2	0.4	1.8
Digestive				
Abdominal discomfort & pain	0.7	0.9	1.7	2.2
Diarrhea	0.9	1.1	1.1	1.4
Gastrointestinal discomfort & pain	0.8	1.9	1.6	2.3
Hyposalivation	1.5	2.1	3.0	3.7
Nausea	7.8	3.9	6.9	10.4
Vomiting	5.7	0.6	3.0	4.0
Musculoskeletal				
Muscle atrophy, weakness & tiredness	0.5	0.2	0.8	3.0
Muscle pain	0.4	1.1	1.5	2.9
Ear, nose & throat				
Nasal signs & symptoms	0.6	0.9	1.0	1.5
Throat & tonsil symptoms	0.4	1.3	1.4	2.4
Respiratory				
Viral infection	0.8	0.6	1.1	1.3
Non-site specific				
Chills	1.3	0.2	0.8	1.2
Malaise/fatigue	1.9	2.6	4.5	9.4
Sensations	2.1	2.6	3.6	5.6
Sweating	0.6	0.4	1.1	1.6

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

Other events observed in association with the administration of RELPAX tablets

The frequencies of less commonly reported adverse clinical events are listed below by body system in order of decreasing frequency. Because the reports include events observed in open studies, the role of **RELPAX** tablets in their causation cannot be reliably determined. Furthermore, variability associated with AE reporting, the terminology used to describe AEs, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=4,719) exposed to **RELPAX**. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug. Frequent AEs are those occurring in at least 1/100 patients, infrequent AEs are those occurring in 1/100 to 1/1,000 patients, and rare AEs are those occurring in fewer than 1/1,000 patients.

General: Frequent: back pain, chills and pain. Infrequent: face edema and malaise. Rare: abdomen enlarged, abscess, accidental injury, allergic reaction, fever, flu syndrome, halitosis, hernia, hypothermia, lab test abnormal, moniliasis, rheumatoid arthritis and shock.

Cardiovascular: Frequent: palpitation. Infrequent: hypertension, migraine, peripheral vascular disorder and tachycardia. Rare: angina pectoris, arrhythmia, atrial fibrillation, AV block, bradycardia, hypotension, syncope, thrombophlebitis, cerebrovascular disorder, vasospasm and ventricular arrhythmia.

Digestive: Infrequent: anorexia, constipation, diarrhea, eructation, esophagitis, flatulence, gastritis, gastrointestinal disorder, glossitis, increased salivation and liver function tests abnormal. Rare: gingivitis, hematemesis, increased appetite, rectal disorder, stomatitis, tongue disorder, tongue edema and tooth disorder.

Endocrine: Rare: goiter, thyroid adenoma and thyroiditis.

Hemic and lymphatic: Rare: anemia, cyanosis, leukopenia, lymphadenopathy, monocytosis and purpura.

Metabolic: Infrequent: creatine phosphokinase increased, edema, peripheral edema and thirst. Rare: alkaline phosphatase increased, bilirubinemia, hyperglycemia, weight gain and weight loss.

Musculoskeletal: Infrequent: arthralgia, arthritis, arthrosis, bone pain, myalgia and myasthenia. Rare: bone neoplasm, joint disorder, myopathy and tenosynovitis.

Neurological: Frequent: hypertonia, hypesthesia and vertigo. Infrequent: abnormal dreams, agitation, anxiety, apathy, ataxia, confusion, depersonalization, depression, emotional lability, euphoria, hyperesthesia, hyperkinesia, incoordination, insomnia, nervousness, speech disorder, stupor, thinking abnormal and tremor. Rare: abnormal gait, amnesia, aphasia, catatonic reaction, dementia, diplopia, dystonia, hallucinations, hemiplegia, hyperalgesia, hypokinesia, hysteria, manic reaction, neuropathy, neurosis, oculogyric crisis, paralysis, psychotic depression, sleep disorder and twitching.

Respiratory: Frequent: pharyngitis. Infrequent: asthma, dyspnea, respiratory disorder, respiratory tract infection, rhinitis, voice alteration and yawn. Rare: bronchitis, choking sensation, cough increased, epistaxis, hiccup, hyperventilation, laryngitis, sinusitis and sputum increased.

Skin and appendages: Frequent: sweating. Infrequent: pruritus, rash and skin disorder. Rare: alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, psoriasis, skin discolouration, skin hypertrophy and urticaria.

Special senses: Infrequent: abnormal vision, conjunctivitis, ear pain, eye pain, lacrimation disorder, photophobia, taste perversion and tinnitus. Rare: abnormality of accommodation, dry eyes, ear disorder, eye hemorrhage, otitis media, parosmia and ptosis.

Urogenital: Infrequent: impotence, polyuria, urinary frequency and urinary tract disorder. Rare: breast pain, kidney pain, leukorrhea, menorrhagia, menstrual disorder and vaginitis.

In post-marketing experience, the following additional undesirable effects have been reported:

Gastro-intestinal disorders: Ischaemic colitis;

Nervous system disorders: Syncope;

Immune system disorders: Allergic reaction, some of which may be serious;

Skin and subcutaneous tissue disorders: Pruritus, rash, urticaria.

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DRUG INTERACTIONS

Effects of other drugs on eletriptan

CYP3A4 inhibitors: *In vitro* studies have shown that eletriptan is metabolized by the CYP3A4 enzyme.

Ketoconazole: A clinical study demonstrated about a 3-fold increase in C_{max} and about a 6-fold increase in the AUC of eletriptan when co-administered with ketoconazole. The half-life of eletriptan increased from 5 h to 8 h and the T_{max} increased from 2.8 h to 5.4 h.

Erythromycin: A clinical study demonstrated about a 2-fold increase in eletriptan C_{max} and about a 4-fold increase in AUC when erythromycin was co-administered with eletriptan. This increased exposure was associated with an increase in eletriptan half-life from 4.6 h to 7.1 h.

Fluconazole: Co-administration of fluconazole and eletriptan yields about a 1.4-fold increase in C_{max} and about a 2-fold increase in AUC of eletriptan.

Verapamil: It has also been shown that co-administration of verapamil and eletriptan yields about a 2-fold increase in C_{max} and about a 3-fold increase in AUC of eletriptan.

Propranolol: The C_{max} and AUC of eletriptan were increased by 10% and 33%, respectively, following an 80 mg BID dose of propranolol administered for 7 days. No interactive increases in blood pressure were observed. No dose adjustment is necessary for patients also taking propranolol.

MAO inhibitors: Eletriptan is not a substrate for monoamine oxidase (MAO) enzymes. Therefore there is no expectation of an interaction between **RELPAX** and MAO inhibitors.

The effect of eletriptan on other drugs

The effect of eletriptan on enzymes other than cytochrome P450 has not been investigated. *In vitro* human liver microsome studies suggest that eletriptan has little potential to inhibit CYP1A2, 2C9, 2E1 and 3A4 at concentrations up to 100 µM. While eletriptan has an effect on CYP2D6 at high concentration (IC_{50} of about 41 µM), this effect should not interfere with metabolism of other drugs when eletriptan is used at recommended doses. There is no *in vitro* or *in vivo* evidence that clinical doses of eletriptan will induce drug metabolizing enzymes. Therefore, eletriptan is unlikely to cause clinically important drug interactions mediated by these enzymes.

Drug-herb interactions

Interactions with herbal products have not been established.

Drug-laboratory interactions

Interactions with laboratory tests have not been established.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms: No significant overdoses in clinical trials have been reported. Twenty-one (21) subjects have received single doses of 120 mg in Phase 1 trials and 427 in Phase 2/3 trials without significant adverse effects. Based on the pharmacology of 5-HT_1 agonists, hypertension or other more serious cardiovascular symptoms could occur on overdose.

Treatment: In case of overdose, standard supportive measures should be adopted. The elimination half-life of eletriptan is about 4 h, and therefore monitoring of patients after overdose with eletriptan should continue for at least 20 h, or longer should symptoms or signs persist. There is no specific antidote to eletriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentration of eletriptan.

For complete prescribing information, please refer to the Product Monograph. The full Product Monograph can be found at: **www.pfizer.ca** or by contacting the Pfizer Canada Inc. Medical Information Services at: **1-800-463-6001**.

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NEUROSURGICAL MONITORING TECHNOLOGIST (CERTIFIED)

Req. #: 110770
Department: Surgery, Section of Neurosurgery
Job Status: Perm/Full Time
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Union: MAHCP
Closing date: Open until filled

Anticipated shift:
Days. If no Technologists (Certified) have applied, consideration may be made to underfill this position with Technician (Uncertified)

Qualifications:
• University Bachelor Degree required. Bachelor of Science Preferred. Registered Electrophysiology Technologist (e.g. EEG, EMG, etc.) preferred.
• Certified by the American Board of Registered Electrodiagnostic Technicians (ABRET) in Neuro Intraoperative Monitoring (CNIM), required.
• CNIM certified by the ABRET required. Registered Electrophysiology Technologist (e.g. EEG, EMG, etc.) and certified by the applicable certifying body, preferred.
• An equivalent combination of education and experience as recognized by the Centre may be considered.
• The ability and initiative to self teach is essential. In addition, the incumbent must attend relevant continuing education programs in operative monitoring, as well as in other related neurodiagnostic areas, on an ongoing basis and as requested by the Neurophysiologist.
• Minimum of one year prior experience as a Neurosurgical Monitoring Technician performing intraoperative monitoring is required.
• Demonstrated ability to communicate effectively both verbally and in writing. Must have excellent interpersonal skills. Ability to function proficiently in the fast paced environment of the O.R.
• Preference will be given to candidates competent in an Aboriginal language and/or knowledge in Aboriginal customs, beliefs, practices.

This position is subject to a Criminal Record Check. The successful candidate will be responsible for any service charges incurred.

Duties:
Under the general direction of the Neurophysiologist, the incumbent performs routine and complex intra and peri-operative neurodiagnostic procedures to identify pertinent neuronal structures. This includes the set up, performance of, and initial interpretation of: Evoked Responses; EMG; EEG; Nerve Conduction Velocity (NCV) and Motor Evoked Potential (MEP) procedures. Provides intraoperative neurophysiological assessments to the clinical team to facilitate optimal neurosurgical outcome. Provides technical and scientific expertise to formulate, submit and conduct research initiatives arising from intraoperative results. Performs additional procedures (e.g. TCDs, CBF, Neuronavigation) as required. Operates, cleans, maintains and troubleshoots equipment.

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CONGRESS SPONSORS

The Canadian Neurological Sciences Federation is pleased to recognize those Sponsors who have already committed to supporting the 2009 Congress. These organizations partner with CNSF to determine the causes of, and develop treatment for diseases and injuries of the nervous system, and in the care of patients with these diseases and injuries. Along with their support of the Canadian Journal of Neurological Sciences and other initiatives the CNSF maintains throughout the year, these organizations graciously provided unrestricted educational grants to the Annual Congress, this year in Halifax, Nova Scotia, June 9-12, 2009.

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Patients with neuropathic pain associated with DPN receiving Cymbalta® demonstrated improvement in the following:‡1

- **Stabbing pain**
  - Cymbalta® 60 mg vs. placebo (56.0% vs. 39.0%; p≤0.05)
  - Cymbalta® 120 mg§ vs. placebo (64.8% vs. 39.0%: p≤0.001)
- **Hot-burning pain**
  - Cymbalta® 60 mg vs. placebo (58.3% vs. 45.2%; p=NS)
  - Cymbalta® 120 mg§ vs. placebo (62.9% vs. 45.2%; p≤0.05)
- **Shooting pain**
  - Cymbalta® 60 mg vs. placebo (53.8% vs. 39.4%; p=NS)
  - Cymbalta® 120 mg§ vs. placebo (61.9% vs. 39.4%; p≤0.001)

Cymbalta® (duloxetine hydrochloride) is indicated for the management of neuropathic pain associated with diabetic peripheral neurpathy (DPN).[2]

Cymbalta® is not indicated for use in children under 18 years of age.[2]

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes. Please see Prescribing Information for complete warnings.[2]

Patients currently taking Cymbalta® should NOT be discontinued abruptly due to risk of discontinuation symptoms. A gradual reduction in the dose is recommended.[2]

Cymbalta® is contraindicated in patients with a known hypersensitivity to the drug or the other components of the product.[2]

Cymbalta® is contraindicated in patients with end-stage renal disease (requiring dialysis) or with severe renal impairment (estimated creatinine clearance <30 mL/min).[2]

Cymbalta® is contraindicated in patients with any liver disease resulting in hepatic impairment.[2]

Cymbalta® is contraindicated in patients concomitantly taking any of the following medications: monoamine oxidase inhibitors; linezolid or within at least 14 days of discontinuing treatment with an MAOI; potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin or enoxacine); and thioridazine.[2]

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta® should not ordinarily be prescribed to patients with substantial alcohol use. Physicians should be aware of the signs and symptoms of liver damage and should investigate such symptoms promptly.[2]

In clinical trials, Cymbalta® was associated with an increased risk of mydriasis; therefore, it is contraindicated in patients with uncontrolled narrow-angle glaucoma.[2]

The most commonly observed adverse events in Cymbalta®-treated patients in placebo-controlled DPN trials (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea (24%), constipation (9%), dry mouth (8%), vomiting (6%), fatigue (12%), decreased appetite (10%), somnolence (17%), and hyperhidrosis (9%).[2]

‡ 12-week, multicenter, double-blind study involving 457 patients experiencing pain due to polyneuropathy caused by Type 1 or Type 2 diabetes mellitus. Patients were randomly assigned to treatment with Cymbalta® 20 mg/d (20 mg QD), 60 mg/d (60 mg QD), 120 mg/d (60 mg BID), or placebo. The primary efficacy measure was the weekly mean score of the 24-h Average Pain Score, which was rated on an 11-point (0–10) Likert scale (no pain to worst possible pain) and computed from diary scores between two site visits. Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to Cymbalta®.[1]

§ 60 mg twice-daily dosing administration[1]

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FOR DIABETIC PERIPHERAL NEUROPATHIC PAIN

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See prescribing summary on pages A-19-22