NEW Electronic Submission

As of December 1, 2007, the Canadian Journal of Neurological Sciences went to an Electronic Submission process. ALL manuscript submissions will be handled by an On-Line tracking system. Go to www.cjns.org and click on SUBMIT YOUR MANUSCRIPT and follow the instructions.

(we will no longer accept paper/disc submissions)

The manuscript submission process is broken into a series of five screens that gather detailed information about your manuscript and allow you to upload the pertinent files. The sequence of screens are as follows:

1. A long form asking for author information, title, abstract, and file quantities.
2. A screen asking for the actual file locations on your computer (via an open file dialog). After completing this screen, your files will be uploaded to our server.
3. A screen requesting the order files should appear in the system-generated merged PDF.
4. A completion screen that will provide you with a specific manuscript number for your manuscript.
5. An approval screen that will allow you to verify that your manuscript was uploaded and converted correctly. You are allowed to replace and delete files, as well as withdraw the manuscript, on this page.

Before submitting a manuscript, please gather the following information:

- All Authors
  - ° First Names, Middle Names/Initials, Last Names
  - ° Institutions
  - ° Departments
  - ° Phone and Fax Numbers
  - ° Street Addresses
  - ° E-mail Addresses
- Title and Running Title (you may copy and paste these from your manuscript)
- Abstract (you may copy and paste this from your manuscript)
- Key words
- Manuscript files in Word, WordPerfect, or Text formats
- Figures/Images in TIF, EPS, PDF, or JPG formats
- Tables in XLS or DOC formats

Kind of figure/File mode/Ideal resolution/ Minimum resolution

Line Bitmap	1200 ppi(ideal) 600 ppi(min)
Color photo CMYK	350 ppi(ideal) 200 ppi(min)
B/W halftone (black and white photo) Grayscale	350 ppi(ideal) 200 ppi(min)
Line/halftone combination	**Grayscale** 600 ppi(ideal) 200 ppi(min)

Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication International Committee of Medical Journal Editors

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. For Uniform Requirements for Sample References go to http://www.nlm.nih.gov/bsd/uniform_requirements.html.

After the manuscript is submitted, you will be asked to select the order you would like the files to be displayed in a merged PDF file that the system will create for you. Next, you will be directed to a page that will allow you to review your converted manuscript. If the conversion is not correct, you can replace or delete your manuscript files as necessary. You may also add additional files at this time. After you have reviewed the converted files, you will need to click on "Approve Converted Files." This link will have a red arrow next to it. Throughout the system, red arrows reflect pending action items that you should address.

Cover Letter

A cover letter is required and must state that the manuscript: has not been published elsewhere, except in abstract form is not under simultaneous consideration by another journal. Once a decision is made by the Editor on your manuscript, the Journal office will send you an Author Release form and a Conflict of Interest form if your manuscript has been accepted for revision.

Abstracts

Original Articles and Case Reports should be accompanied by an abstract of 250 words or less on a separate page, in either English or French. The Journal will provide translation to the other language if required. Abstracts should consist of four paragraphs headed: Background (or Objective), Methods, Results and Conclusions.

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.

References

References should be numbered in the order of their citation in the text. Those cited only in tables and legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration.

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 and authors must provide five copies of "submitted" manuscripts.

Avoid "personal communications" and, if necessary, include them in the body of the text, not among the references. Reference citations should not include unpublished presentations or other non-accessible material. Books or chapter references should also include the place of publication and the name of the publisher.

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

Examples of correct forms of reference:

Journals

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

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

Review Articles

Review articles on selected topics are also published. They are usually invited, but unsolicited reviews will be considered. Review articles should be accompanied by an abstract of 150 words or less.

Brief Correspondence (formerly Peer Reviewed Letters)

Brief Correspondence articles to the Editor are published on various topics. The articles should be limited to approximately six double-spaced manuscript pages (2-3 Journal pages) and may include illustrations and tables.

Editor Correspondence

Correspondence to the Editor concerning matters arising in recent articles are welcome. Correspondence should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

Neuroimaging Highlights

Neuroimaging highlights are selected by the editor-in-chief and neuroimaging highlight editors on the basis of two factors. The first is high quality "state of the art" imaging of a novel and uncommon (or common with an uncommon twist) neurological or neurosurgical disorder. The second factor is the clinical novelty of the case.

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 highlights should be 500 words or less, with no more than 10 references.

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

Suitability for publication is judged by the neuroimaging highlight editors, the editor-in-chief and up to one additional external referee.

Reflections

Neuroimaging highlights are selected by the editor-in-chief and neuroimaging highlight editors on the

Permissions and Releases

Any non-original material (quotations, tables, figures) must be accompanied by written permission from the author and the copyright owner to reproduce the material in the Journal. Photographs of recognizable persons must be accompanied by a signed release from the legal guardian or patient authorizing publication.

Conflict of Interest

Authors who have non-scientific or non-academic gain, whether it be financial or other, from publishing their article are responsible for declaring it to the Editor. Any financial interest, research grant, material support, or consulting fee associated with the contents of the manuscript must be declared to the Editor. These guidelines apply to each author and their immediate families. Conflicts of interest are not necessarily wrong, nor do they necessarily change the scientific validity of research or opinion, but the Journal and readers should be aware of the conflict. If the Editor considers the conflict to compromise the validity of the paper, it will not be accepted for publication.

Authors, editorial staff and reviewers are asked to declare any relationship that would be considered as a conflict of interest whether or not they believe that a conflict actually exists. Information that the Journal receives about conflict or potential conflict will be kept confidential unless the Editor or Associate Editor considers it to be important to readers. Such conflicts will be published in the author credits or as a footnote to the paper, with knowledge of the authors.

Getting Help

If you need additional help, you can click on the help signs spread throughout the system. A help dialog will pop up with context-sensitive help.

Manuscript Status

After you approve your manuscript, you are finished with the submission process. You can access the status of your manuscript at any time via:

1. Logging into the system with your password
2. Clicking on the link represented by your manuscript tracking number and abbreviated title
3. Clicking on the "Check Status" link at the bottom of the displayed page

   This procedure will display detailed tracking information about where your manuscript is in the submission/peer-review process.

Starting

The manuscript submission process starts by pressing the "Submit Manuscript" link on your "Home" page (www.cjns.org). Please make sure you have gathered all the required manuscript information listed above BEFORE starting the submission process.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

CALENDAR OF EVENTS

March 9-10, 2009
Toronto, Ontario, Canada
19th Annual Rotman Research Institute Conference - Cognitive Aging: Research and Practice
For additional information, please visit our web-site: http://www.rotman-baycrest.on.ca or queries can be directed to (416) 785-2500 ext. 2363 or e-mail pferreira@baycrest.org.

March 11-14, 2009
Victoria, British Columbia, Canada
3rd International Conference on Fetal Alcohol Spectrum Disorder Integrating Research, Policy and Promising Practice Around the World: A Catalyst for Change
Register before the Early Bird Deadline of January 12, 2009 to take advantage of the reduced rate. Telephone (604) 822-7524 or Toll-free within BC: 1-877-328-7744; Fax: (604) 822-4835 OR Via E-Mail: jpad@interchange.ubc.ca or go to our website at www.peopleware.net/index.cfm?siteCode=1268.

March 11-15, 2009
Prague, Czech Republic
9th International Conference - Alzheimer's & Paarkinson's Diseases: Advances, Concepts & New Challenges
For more information or to register, please visit www.kenes.com/adpd

March 12-15, 2009
Chongqing, China
China Chongqing International Neurological Forum 2009
For more information, contact Yao Lu (C) 001-514-347-6758 or email epsworldlink@gmail.com or visit our website at epsworldlink.com

March 27-31, 2009
Marseille, France
Marseille Neurosurgery 2009 Joint Annual Meeting (EANS-SFNC)
For information, please visit our website at: www.kenes.com/eans-sfnc.

April 2-4, 2009
Washington, DC, USA
2nd International Conference on Psychogenic Movement Disorders and Other Conversion Disorders
For more information, please visit our website at: www.movementdisorders.org/education/pmd

April 15-18, 2009
Rotterdam, The Netherlands
9th European Skull Base Society Meeting
For more information, please visit our website at: www.esbs2009.eu.

April 25-28, 2009
Rome, Italy
XI International Facial Nerve Symposium
For more information go to www.facialnerve2009.org.

April 25 - May 2, 2009
Seattle, Washington, USA
AAN Annual Meeting
For information go to: www.aan.com

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.

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 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 7-10, 2009
Toronto, Ontario, Canada
SickKids Centre for Brain & Behaviour 1st Annual International Symposium
Visit www.sickkids.ca/learninginstitute or email li.conferences@sickkids.ca.

July 17-18, 2009
St. John's, Newfoundland, Canada
Canadian Radiosurgery Society Meeting (CaRS)
For more information please visit our site: www.canadianradiosurgery.com

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)
For more information or to register, please visit www.AANS.org/wfns2009 or email wfns2009@aans.org

October 8-11, 2009
Prague, The Czech Republic
3rd World Congress on Controversies in Neurology (CONy)
For more information please visit our site: http://comtecmed.com/cony/2009/

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

Maxalt®

rizatriptan benzoate tablets

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

(~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.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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.

1130-a, 3, 08

34381016

PRODUCT MONOGRAPH AVAILABLE AT
www.merckfrosst.com
OR UPON REQUEST AT 1-800-567-2594

MERCK FROSST
Discovering today for a better tomorrow.

Member R&D

MERCK FROSST CANADA LTD.
P.O. BOX 1005, POINTE-CLAIRE
DORVAL, QUEBEC H9R 4P8

PAAB

See our AD on page A-7

Cymbalta® DELAYED RELEASE CAPSULES
duloxetine HCl

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.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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]

	Percentage of Patients Reporting Event			
System Organ Class/ Adverse 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

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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				
Pollakiuria	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
duloxetine HCl

Member R&D PAAB

Boehringer Ingelheim Lilly

ADVERTISERS INDEX

Calendar of Events	A-12
Classified Ads	A-11
Board of Directors/ Committee Chairs	A-31
CNSF Preliminary Program	A-28
Information for Authors	A-9, A-10
CNSF Sponsors	IBC
Boehringer Ingelheim/Lilly	
Cymbalta	A-5, A-17-20
Elekta	IFC
Merck Frosst	
Maxalt	A-7, A-13-16
Pfizer	
Lyrica	A-8, A-29-30
Teva Neuroscience	
Azilect	A-6, A-23-26
Copaxone	OBC, A-21-22

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

See our AD on page A-5

COPAXONE®
(glatiramer acetate injection)

Treating RRMS for the long run.

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: *Immunomodulator*

INDICATIONS AND CLINICAL USE

COPAXONE® (glatiramer acetate injection) is indicated for use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis (RRMS) to reduce the frequency of relapses. The safety and efficacy of COPAXONE® in chronic progressive MS has not been established.

CONTRAINDICATIONS

COPAXONE® (glatiramer acetate injection) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

Safety Information

WARNINGS

The only recommended route of administration of COPAXONE® (glatiramer acetate injection) is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Symptoms of Potentially Cardiac Origin: Approximately 26% of COPAXONE® patients in the pre-marketing multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see ADVERSE REACTIONS: Chest Pain). While some of these episodes occurred in the context of the Immediate post-injection reaction (see ADVERSE REACTIONS: Immediate Post-Injection Reaction), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an immediate post-injection reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see ADVERSE REACTIONS: Immediate Post-Injection Reaction).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

PRECAUTIONS

General: Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate injection) (see INFORMATION FOR THE PATIENT). The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: **COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's *defenses against infections and tumor surveillance. Systematic assessments of these risks have not been* done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.**

Glatiramer acetate reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RRMS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested.

Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and therefore, this risk cannot be excluded.

Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice. The relevance of these findings for humans is unknown (see PRECAUTIONS: Considerations Involving the Use of a Product Capable of Modifying Immune Responses).

Information for Patients: To assure safe and effective use of COPAXONE®, the following information and instructions should be given to the patients:

1. COPAXONE® is not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Inform your physician if you stop taking the drug.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE®.

Appropriate instructions for the self-injection of COPAXONE® should be given, including a careful review of the INFORMATION FOR THE PATIENT. The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures.

Awareness of Adverse Reactions: *Physicians are advised to counsel patients about adverse reactions* associated with the use of COPAXONE® (see ADVERSE REACTIONS). In addition, patients should be advised to read the INFORMATION FOR THE PATIENT and resolve any questions regarding it prior to beginning COPAXONE® therapy. **Drug Interactions:** Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial, did not report any serious or unexpected adverse events thought to be related to treatment. **Laboratory Tests:** Data collected pre- and post-market do not suggest the need for routine laboratory monitoring. **Use in Pregnancy:** There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre-marketing clinical trials with COPAXONE®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE® should only be considered after careful risk/benefit assessment and be used with caution. **Use in Children:** The safety and effectiveness of *COPAXONE® have not been established in individuals below 18 years of age.* **Use in the Elderly:** *COPAXONE®* has not been studied in the elderly (> 65 years old). **Use in Patients with Impaired Renal Function:** The pharmacokinetics of COPAXONE® in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in double-blind controlled clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), with a subset of patients (n = 108) continuing up to 10 years in open-label extensions at a daily dose of 20 mg. In controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® *which occurred at a higher frequency than in placebo-treated patients were: injection-site reactions, vasodilation,* chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia.

Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were (in order of descending frequency): injection-site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE® in pre-marketing studies reported a post-injection reaction immediately following subcutaneous *injection of COPAXONE®. Symptoms experienced could include flushing, chest pain, palpitations, anxiety,* dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see WARNINGS).

Chest Pain: Approximately 26% of glatiramer acetate patients in the multicenter pre-marketing controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the immediate post-injection reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. There has been only one episode of chest pain during which a full ECG was performed; the ECG showed no evidence of ischemia. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see WARNINGS: Symptoms of Potentially Cardiac Origin).

ADMINISTRATION

DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis. The recommended dose of COPAXONE® (glatiramer acetate injection) for the treatment of Relapsing-Remitting MS is a daily injection of 20 mg given subcutaneously. For the pre-filled syringe of COPAXONE®, please see the INFORMATION FOR THE PATIENT – pre-filled syringe for instructions on the preparation and injection of COPAXONE®.

SUPPLEMENTAL PRODUCT INFORMATION

ADVERSE REACTIONS

Table 1 lists the adverse experiences after up to 35 months of treatment (> 27-33 months: COPAXONE®, n=84; Placebo, n=75; > 33 months: COPAXONE®, n=12; Placebo, n=24) in the pre-marketing multicenter placebo controlled study (Trial II) in Relapsing-Remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE® and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported.

It should be noted that the figures cited in Table 1 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1: Pre-marketing Controlled Trial in Patients with Multiple Sclerosis Adverse Experiences ≥2% Incidence and ≥2% Above Placebo

		Copaxone® (n=125)		Placebo (n=126)	
Adverse Experience		N	%	N	%
Body as a Whole	Injection-Site Pain	83	66.4	46	36.5
	Asthenia	81	64.8	78	61.9
	Injection-Site Erythema	73	58.4	17	13.5
	Injection-Site Pruritus	48	38.4	5	4.0
	Flu syndrome	38	30.4	34	27.0
	Injection-Site Inflammation	35	28.0	9	7.1
	Back pain	33	26.4	28	22.2
	Chest pain	33	26.4	13	10.3
	Injection-Site Mass	33	26.4	10	7.9
	Injection-Site Induration	25	20.0	1	0.8
	Injection-Site Welt	19	15.2	5	4.0
	Neck pain	16	12.8	9	7.1
	Face Edema	11	8.8	2	1.6
	Injection-Site Urticaria	9	7.2	0	0
	Injection-Site Hemorrhage	8	6.4	4	3.2
	Chills	5	4.0	1	0.8
	Cyst	5	4.0	1	0.8
	Injection-Site Reaction	4	3.2	1	0.8
	Injection-Site Atrophy	3	2.4	0	0
	Abscess	3	2.4	0	0
Cardiovascular	Vasodilatation	34	27.2	14	11.1
	Palpitation	14	11.2	6	4.8
	Migraine	9	7.2	5	4.0
	Syncope	8	6.4	4	3.2
Digestive	Nausea	29	23.2	22	17.5
	Vomiting	13	10.4	7	5.6
	Anorexia	6	4.8	3	2.4
	Gastroenteritis	6	4.8	2	1.6
	Oral Moniliasis	3	2.4	0	0
	Tooth Caries	3	2.4	0	0
Hemic and Lymphatic	Lymphadenopathy	23	18.4	12	9.5
	Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional	Peripheral Edema	14	11.2	7	5.6
	Weight gain	7	5.6	0	0
	Edema	5	4.0	1	0.8
Musculo Skeletal	Arthralgia	31	24.8	22	17.5
	Hypertonia	44	35.2	37	29.4
	Tremor	14	11.2	7	5.6
	Agitation	7	5.6	4	3.2
	Confusion	5	4.0	1	0.8
	Nystagmus	5	4.0	2	1.6
Respiratory	Rhinitis	29	23.2	26	20.6
	Dyspnea	23	18.4	8	6.4
	Bronchitis	18	14.4	12	9.5
Skin and Appendages	Sweating	15	12.0	10	7.9
	Erythema	8	6.4	4	3.2
	Skin Disorder	5	4.0	2	1.6
	Skin Nodule	4	3.2	1	0.8
	Wart	3	2.4	0	0
Special Senses	Ear Pain	15	12.0	12	9.5
	Eye Disorder	8	6.4	1	0.8
Urogenital System	Urinary Urgency	20	16.0	17	13.5
	Vaginal Moniliasis	16	12.8	9	7.1
	Dysmenorrhea	12	9.6	9	7.1
	Unintended Pregnancy	4	3.2	0	0
	Impotence	3	2.4	0	0

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included:

Body as a whole: Headache, injection-site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise. *Digestive system:* Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth. *Musculoskeletal:* Myasthenia and myalgia. *Nervous system:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder. *Respiratory System:* Pharyngitis, sinusitis, increased cough and laryngitis. *Skin and Appendages:* Acne, alopecia, and nail disorder. *Special Senses:* Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness. *Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any trial due to abnormal laboratory findings.

Other Adverse Events Observed During All Clinical Trials: COPAXONE® has been administered to approximately 900 individuals during clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. 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 those occurring in 1/100 to 1/1000 patients. *Body as a whole: Frequent:* injection-site edema, injection-site atrophy, abscess and injection-site hypersensitivity. *Infrequent:* injection-site hematoma, injection-site fibrosis, moon face, cellulitis, generalized edema, hernia, injection-site abscess, serum sickness, suicide attempt, injection-site hypertrophy, injection-site melanosis, lipoma and photosensitivity reaction. *Cardiovascular: Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins, hypotension and varicose veins. *Digestive: Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration and duodenal ulcer. *Endocrine: Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. *Gastrointestinal: Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. *Hemic and Lymphatic: Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. *Metabolic and Nutritional: Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. *Musculoskeletal: Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. *Nervous: Frequent:* Abnormal dreams, emotional lability, and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. *Respiratory: Frequent:* Hyperventilation, hay-fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. *Skin and Appendages: Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. *Special Senses: Frequent:* Visual field defect. Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. *Urogenital: Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Adverse events reported post-marketing and not previously noted in clinical trials: Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate) not mentioned above, that have been received since market introduction and that may have or not have causal relationship to the drug include the following: *Body as a Whole:* Sepsis, LE syndrome, hydrocephalus, enlarged abdomen, injection-site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. *Cardiovascular:* Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy cardiomegaly, arrhythmia, angina pectoris, tachycardia. *Digestive:* Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. *Hemic and Lymphatic:* Thrombocytopenia, lymphoma-like reaction, acute leukemia. *Metabolic and Nutritional:* Hypercholesteremia. *Musculoskeletal:* Rheumatoid arthritis, generalized spasm. *Nervous:* Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. *Respiratory:* Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. *Skin and Appendages:* Herpes simplex, pruritis, rash, urticaria. *Special Senses:* Glaucoma, blindness, visual field defect. *Urogenital:* Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency. **Localized Adverse Reactions Associated with subcutaneous use:** At injection sites, localized lipoatrophy and, rarely, injection-site skin necrosis have been reported during post-marketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis. (see INFORMATION FOR THE PATIENT)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow up several hours later produced no report of adverse experiences from either patient. The maximum COPAXONE® dose reported in an overdose case is 80 mg glatiramer acetate injection.

Based on Product Monograph dated April 2, 2008. Product Monograph available on request.

TEVA NEUROSCIENCE

PAAB

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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)

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

See our AD on page A-6

Thank you to our Reviewers

We are indebted to the expert referees who have reviewed submissions to the Canadian Journal of Neurological Sciences in 2008 (names in bold reviewed five or more papers). Their thoughtfulness and expertise have served our journal well.

Name
Adams, Harold
Agid, Ronit
Ajlan, Abdulrazag
Ang, Lee-Cyn
Anisman, Hymie
Armstrong, John
Asheghan, Mahsa
Aube, Michel
Auer, Roland
Aviv, Richard
Bailey, Peter
Baker, Steven
Becker, Werner
Benavente, Oscar
Benstead, Timothy
Berger, Leo
Bernstein, Mark
Bhan, Virender
Bharatha, Aditya
Blume, Warren
Bocti, Christian
Borrie, Michael
Bouchard, Jean-Pierre
Bouchard, Remi
Boulanger, Jean-Martin
Bray, Garth
Bril, Vera
Brown, Authur
Brown, W.F.
Brownell, Keith
Brunet, Donald
Bruni, Joseph
Buncic, Joseph
Burneo, Jorge
Bussiere, Miguel
Butcher, Ken
Cardenas, Graciela
Camfield, Peter
Camicioli, Richard
Campbell, Craig
Cansever, Tufan
Caplan, Louis
Carlen, Peter
Carter, Cedric
Casha, Steven
Cashman, Neil
Cengiz, Sahika
Chakraborty, Santanu
Chalk, Colin
Chan, Ming
Chan, Richard
Chapman, Ken
Chen, Robert
Chouinard, Sylvain
Chow, Michael
Christie, Sean
Clarke, David
Connolly, Mary
Cooke, Lara
Cooper, Paul
Coupland, Stuart
Cregan, Sean
Curt, Armin
D'Amour, Monique
Darvesh, Sultan
De Man, Joris
De Vera, Nuria
Del Campo, Martin
Demaerschalk, Bart
Derry, Paul
Desbiens, Richard
Diosy, David
Doja, Asif
Dos Santos, Marlise
Dunham, Christopher
Dupre, Nicolas
Duquette, Pierre
Elleker, George
Erdogan, Ersin
Farb, Richard
Feng, Zhong-Ping
Ferguson, Gary
Fewer, Derek
Findlay, J Max
Fleetwood, Ian
Fleming, Ross
Fortin, David
Fouad, Karim
Fourney, Daryl
Fox, Allan
Fox, Richard
Fox, Susan
Freedman, Mark
Gauthier, Serge
Gibb, Robin
Goodridge, Alan
Gordon, Allan
Gordon, Kevin
Gotman, Jean
Goyal, Mayank
Grand'Maison, Francois
Grant, Ian
Grimes, David
Guberman, Alan
Guttman, Mark
Hader, Walter
Hadjivassiliou, Marios
Hakan, Tayfun
Hamilton, Mark
Hammond, Robert
Heidari, Mohammad
Mehdi
Herrmann, Nathan
Hill, Alan
Hill, Michael
Hodaie, Mojgan
Hogan, David
Holness, Renn
Howard, Peter
Howse, David
Hsiung, Ging-Yuek
Hudon, Mark
Hudson, Arthur
Hurlbert, R. John
Hwang, Paul
Islam, Omar
Jackson, Alan
Jacobson, Mark
Jacova, Claudia
Jenkins, Mary
Jette, Nathalie
Jichici, Draga
Joffe, Ari
Johnston, Wendy
Joseph, Elizabeth
Jousmaki, Veikko
Karimi, Soheila
Karlik, Stephen
Kawarai, Toshitaka
Keene, Daniel
Kertesz, Andrew
Kirk, Andrew
Kirton, Adam
Kondziolka, Douglas
Koo, Betty
Krings, Timo
Kurzepa, Jacek
Lachance, Daniel
Lafontaine, Anne-Louise
Laforce, Robert
Lagerlund, Terrence
Lapierre, Yves
Larrazabal, Ramiro
Leasa, David
Leavitt, Jacqueline
Lee, Robert
Levin, Simon
Little, Julian
Lo, Benjamin
Lo, Y.L.
Logan, William
Longman, Stewart
Lowry, Noel
Lum, Cheemun
Lysack, John
Macaulay, Robert
Macdonald, Loch
MacKnight, Chris
Markanday, Anurag
Marotta, Tom
Martin, Wayne
Massoud, Fadi
Mathieu, Jean
Mayo, Nancy
McDonald, Patrick
Meakin, Susan
Megyesi, Joseph
Mehta, Vivek
Melanson, Michel
Mendis, Tilak
Midroni, Gyl
Mikulis, David
Mirsattari, Seyed
Montanera, Walter
Moore, David
Moore, Fraser
Morrish, William
Murray, Jock
Nag, Sukriti
Nataraj, Andrew
Norton, Jonathan
Nguyen-Huynh, Mai
O'Connor, Paul
Oger, Joel
Pang, Elizabeth
Panisset, Michel
Pasternak, Stephen
Paulseth, J.E. Rick
Payne, David
Pelz, David
Perry, James
Phillips, Stephen
Poulter, Michael
Prasad, Asuri
Prasad, Narayan
Pringle, Catherine
Rabinovitch, Daniel
Rajput, Alex
Rao, Ganesh
Raybaud, Charles
Raymond, Jean
Redekop, Gary
Richer, Lawrence
Robertson, Janice
Rodenhiser, David
Roman, Gustavo
Ronen, Gabriel
Ross, Owen
Rossiter, John
Rouleau, Guy
Rumbaugh, Jeffrey
Sadler, Mark
Saposnik, Gustavo
Sarma, Dipanka
Sarnat, Harvey
Schmidt, Matthias
Schondorf, Ronald
Schwartz, Michael
Scott, James
Scott, Shannon
Seetharam, Raghavendra
Seigel, G.
Seland, Peter
Seshia, Shashi
Shah, Namrata
Shahin, Antoine
Shemie, Sam
Shoesmith, Christen
Shroff, Manu
Shuaib, Ashfaq
Silver, Brian
Simpson, David
Sinclair, Barry
Spacey, Sian
Spears, Julian
Spence, J. David
Steven, David
Stewart, Dwight
Suchowersky, Oksana
Symons, Sean
Tarnopolsky, Mark
Tator, Charles
Tay, Keng
Teitelbaum, Jeanne
Tellez-Zenteno, Jose
ten Hove, Martin
ter Brugge, Karel
Tervaniemi, Mari
Tetzlaff, Wolfram
Toth, Cory
Toyota, Brian
Tremblay, Francois
Vandorpe, Robert
Veilleux, Martin
Venance, Shannon
Wang, Jianping
Warren, Sharon
Watson, Tim
Webster, Peter
Wee, Roberto
Wein, Theodore
West, Michael
Wheatley, Matt
Wheelock, Brian
Wherrett, John
White, Chris
Whiting, Sharon
Wiebe, Samuel
Willinsky, Robert
Wong, John
Woulfe, John
Yan, Jun
Younge, Brian
Yu, Eugene
Zhang, Xiangjian
Zochodne, Douglas

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

Canadian Neurological Sciences Federation
44th Annual Congress

Preliminary Program (Tentative)
as at January 27th, 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
8:00 - 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
12:00 - 1:30	Co-developed Industry Symposium
12:00 - 1:30	Co-developed Industry Symposium
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: Jeanne Teitelbaum***
1:30 - 5:00	Epilepsy ***Chairs: Francois Dubeau***
1:30 - 5:00	EMG ***Chairs: Ian Grant and Timothy Benstead***
1:30 - 5:00	Neuro-ophthalmology ***Chair: William Fletcher***
5:00 – 6:30	Sponsors and Exhibitors Reception
6:30 – 8:00	Co-developed Industry Symposium

Thursday, June 11/09

8:00 - 9:30	Plenary-CNS, CACN & CSCN ***Michael Sinnreich–Gloor/Brenda Banwell-Tibbles***
8:00 - 9:30	Plenary-CNSS ***Michael West/Gary Steinberg-Penfield***
9:30 -10:00	Coffee Break
10:00 - 12:15	Platforms (7 simultaneous)
12:15 - 2:00	Lunch/Exhibit Viewing/Digital Mini-platforms
2:00 - 4:30	Platforms (7 simultaneous)
4:30 - 5:30	Digital Poster and Exhibit Viewing
6:00 - 8:00	Maritime Lobster Supper and Kitchen Party

Friday, June 12/09

8:00 - 9:00	Distinguished guest lecture (TBD)
9:00 - 9:15	Journal Editor's Report
9:15 - 9:30	CBANHC Report
9:30 - 10:15	Coffee break/Exhibit viewing
10:15 - 12:00	Grand Rounds
12:00 - 1:30	Lunch / Exhibit viewing / Digital Mini-platforms
1:30 - 5:00	Peripheral Nerve ***Chair: Raj Midha***
1:30 - 5:00	What's New in Neurosurgery? ***Chair: Ian Fleetwood***
1:30 - 5:00	EEG ***Chair: Seyed Mirsattari***
1:30 - 5:00	Endoscopy ***Chair: Mark Hamilton***
1:30 - 5:00	Dementia ***Chair: Sultan Darvesh***
1:30 - 5:00	What's New in Neurology? ***Chair: Roger McKelvey***
1:30 - 5:00	MS ***Chair: Virender Bhan***

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

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

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.

Pfizer

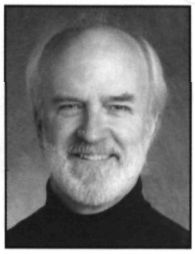
Working together for a healthier world™

See our AD on page A-8

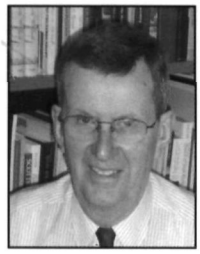
CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

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

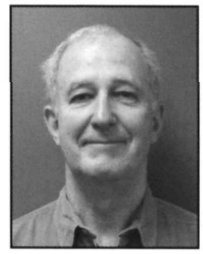
2008 – 2009 Board of Directors and Committee Chairs



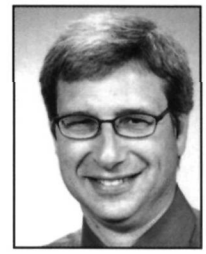
George Elleker
- *CNSF President*
- *NSFC President*
- *CSCN Past President*



Garth Bray
- *CNSF Vice-President*
- *NSFC Vice-President*
- *CNS Member*



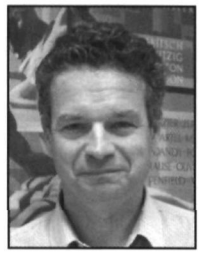
Derek Fewer
- *CNSF Vice-President*
- *NSFC Vice-President*
- *CNSS Past President*



Jerome Yager
- *CNSF Board Member*
- *NSFC Board Member*
- *CACN President*

Mary Connolly
- *CNSF Board Member*
- *NSFC Board Member*
- *CACN Vice-President*

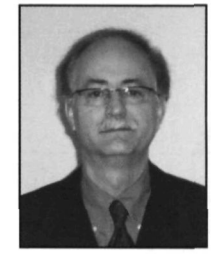
J. Max Findlay
- *CNSF Board Member*
- *NSFC Board Member*
- *CNSS President*



Chris Wallace
- *CNSF Board Member*
- *NSFC Board Member*
- *CNSS Vice-President*

Richard Desbiens
- *CNSF Board Member*
- *NSFC Board Member*
- *CNS President*

Lyle Weston
- *CNSF Board Member*
- *NSFC Board Member*
- *CNS Vice- President*



Manouchehr Javidan
- *CNSF Board Member*
- *NSFC Board Member*
- *CSCN President*

Ming Chan
- *CNSF Board Member*
- *NSFC Board Member*
- *CSCN Vice-President*

Teneille Gofton
- *CNSF Board Member*
- *NSFC Board Member*
- *Residents' Rep. CNS*

Gregory Hawryluk
- *Residents' Rep. CNSS*

Vijay Ramaswamy
- *Residents' Rep. CACN*

Andrew Kirk
- *CNSF/NSFC Past President*
- *Non-voting*

Dan Morin
- *CEO*

Non-voting

G. Bryan Young
- *Journal Editor-in-chief*
- *CNS & CSCN Member*

Mike Tymianski
- *CNSF Scientific Program Committee Chair*
- *CNSS Member*

Brian Wheelock
- *CNSF Professional Development Committee Chair*
- *CNSS Member*

Richard Riopelle
- *CBANHC Chair*

Legend:
CNSF - *Canadian Neurological Sciences Federation;* NSFC - *Neurological Sciences Foundation of Canada;* CNS - *Canadian Neurological Society;* CNSS - *Canadian Neurosurgical Society;* CSCN - *Canadian Society of Clinical Neurophysiologists;* CACN - *Canadian Association of Child Neurology;* CBANHC - *Canadian Brain and Nerve Health Coalition*

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

NOTES

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

EARLY COMMITTED SPONSORS FOR 2009

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 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.

GOLD

Pfizer

SILVER

sanofi aventis
Because health matters

MERCK FROSST
Discovering today
for a better tomorrow.

ucb

Boehringer Ingelheim

Lilly

BRONZE

TEVA NEUROSCIENCE

Medtronic

CONGRESS SPONSORSHIP AND EXHIBITOR OPPORTUNITIES

The Canadian Neurological Sciences Federation's Congress is the largest educational forum and industry show in the country for neurologists, neurosurgeons, child neurologists, neuroradiologists and neurophysiologists. Representing the largest and most diverse neuro-specialist groups in Canada, the Halifax Congress in June 2009 will again feature exceptionally strong science and hold undeniable corporate value for our industry partners.

If you and your organization would like more information, or would like to discuss how you can partner with CNSF and meaningfully connect with our Congress delegates, please call or email Brett Windle, Corporate Development Coordinator at (403) 229-9544 or brett-windle@cnsfederation.org

Join Canada's pharmaceutical and equipment manufacturing leaders in the neurosciences by showing your support for continuing education and lifelong learning.

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

https://doi.org/10.1017/S0317167100117512 Published online by Cambridge University Press

For brief prescribing information see page A-21-22