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- Key words
- Manuscript files in Word, WordPerfect, or Text formats
- Figures/Images in TIF, EPS, PDF, or JPG formats
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Please Note:

A title page should identify the title of the article, authors, name of institution(s) from which the work originated and the address, telephone and fax numbers of the corresponding author. Pages of text should be numbered consecutively. All manuscripts must be double spaced throughout including references and legends for illustrations.

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

Line Bitmap	1200 ppi(ideal) 600 ppi(min)
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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 and papers should be double-spaced. For Uniform Requirements for Sample References go to http://www.nlm.nih.gov/ bsd/uniform_requirements.html.

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A cover letter is required and must state that the manuscript: has not been published elsewhere, except in abstract form and 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 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.

Acronyms

Journal standards state that a sentence must not start with an acronym. Also please define any undefined acronyms in your manuscript in a list as well as inserting the definition with its acronym where it is first used in the text. If the word is not used a minimum of 3 times throughout the manuscript, an acronym will not be necessary as the long form will be used.

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.

INFORMATION FOR AUTHORS / SUBMISSION PROCESS

(continued)

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

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

Chapter in a book

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

Tables

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 unstructured abstract of 150 words or less.

Brief Communications (Case Reports)

Brief Communications 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 Highlight should be 500 words or less, with no more than 10 references.

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

Reflections

As witnesses to and participants in the most poignant of human dramas and ethical dilemmas, we invite essays, poems or stories for our new Reflections section from students, residents and "veteran" clinicians. Clinicians and students are often so preoccupied with workloads and committments that the human aspects are often insufficiently appreciated. Please send us your reflections in 1500 words or less.

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2. Clicking on the link represented by your manuscript tracking number and abbreviated title.
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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.

ADVERTISERS INDEX

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CALENDAR OF EVENTS

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 26-29, 2009
Boston, Massachusetts, USA
6th Annual World Congress for Brain Mapping and Image Guided Therapy
Call for Papers - Abstract Submission Deadline: March 27, 2009.
For more information go to: www.ibmisps-worldcongress.org

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

August 30-September 4, 2009
Boston, Massachusetts, USA
XIV Congress of the World Federation of Neurosurgical Societies (WFNS)
For more information or to register, please visit
www.AANS.org/wfns2009 or email wfns2009@aans.org

September 11-12, 2009
Toronto, Ontario
10th Annual Interventional Neuroradiology Symposium
For additional information: Website: www.cme.utoronto.ca
Email: info-MIM0904@cmetoronto.ca

September 12-15, 2009
Florence, Italy
13th Congress of The European Federation of Neurological Societies
For additional information, please visit our web-site:
www.efns.org/efns2009 or e-mail florence2009@efns.org.

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

October 1 - 3, 2009
Toronto, Ontario
5th Canadian Conference on Dementia
For more information please visit our site: www.ccd2009.ca/

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

October 9 - 10, 2009
Zenith of Rouen, France
1st European Congress on Environmental Pathologies
For more information please visit our site: www.ecep2009.eu

October 15-16, 2009
Valencia, Spain
International Symposium on Neurorehabilitation. From Basics to Future
For information about our Congress, please go to our website:
www.neurorehabilitationvalencia.es.

October 17, 2009
Toronto, Ontario
International Next Generation Eye Surgery, Device and Drug Delivery Symposium
For more information visit our website:
http://events.cmetoronto.ca/website/index/OPT0906

October 19-23, 2009
Gauteng, South Africa
2nd Paediatric Neuropsychology Symposium
For information on the speakers and the full programme please visit the website: www.tegmentum.co.za

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Cymbalta® DELAYED RELEASE
duloxetine HCl CAPSULES

30 mg and 60 mg Delayed-release Capsules

Prescribing Summary

Patient Selection Criteria

Analgesic

INDICATIONS

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

CONTRAINDICATIONS

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

Monoamine Oxidase Inhibitors (MAOIs)

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

Hepatic Impairment

CYMBALTA™ is contraindicated in patients with any liver disease resulting in hepatic impairment.

Uncontrolled Narrow-angle Glaucoma

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

Severe Renal Impairment

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

Thioridazine

Concomitant use of CYMBALTA™ and thioridazine is contraindicated.

CYP1A2 Inhibitors

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

USE IN SPECIAL POPULATIONS

Use in Pregnant Women:

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

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

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

Use in Nursing Women:

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

Use in Pediatrics (<18 years of age):

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

Use in Geriatrics (≥65 years of age):

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

Use in Patients with Substantial Alcohol Use:

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

Safety Information

WARNINGS AND PRECAUTIONS

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

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

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

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

Discontinuation Symptoms

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

Monoamine Oxidase Inhibitors (MAOI):

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

Hepatic Impairment:

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

Hepatotoxicity:

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

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

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

Controlled Narrow-angle Glaucoma:

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

Thioridazine:

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

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

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

Cardiovascular:

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

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

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

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

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

Dependence:

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

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

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

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

Endocrine:

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

Hematologic:

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

Neurologic:

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

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

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

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

Psychiatric:

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

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

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

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

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

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

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

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

Post-market Adverse Drug Reactions

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

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

Drug Interactions:

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2:

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

Inhibitors of CYP2D6:

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

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP2D6:

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

Drugs Metabolized by CYP1A2:

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

Drugs Highly Bound to Plasma Protein:

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

CNS Drugs:

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

Serotonergic Drugs:

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

Triptans (5HT1 agonists):

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

Tricyclic Antidepressants (TCA):

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

Warfarin:

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

Drugs that Affect Gastric Acidity:

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

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

Administration

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

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

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy:

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

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

Patients with Renal Impairment:

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

Patients with Hepatic Impairment:

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

Elderly Patients:

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

Treatment of Pregnant Women During the Third Trimester:

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

Discontinuation of Treatment:

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

Switching Patients to or from a Monoamine Oxidase Inhibitor:

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

Study References

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

Supplemental Product Information

Adverse Reactions:

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

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

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System Organ Class/ Adverse Event	Percentage of Patients Reporting Event			
	CYMBALTA® 60 mg QD (N=344)	CYMBALTA® 60 mg BID (N=341)	CYMBALTA® Total* (N=800)	Placebo (N=339)
Nervous System Disorder				
Somnolence[7]	17	21	17	5
Headache	12	11	12	9
Dizziness	11	13	11	6
Parathesia[8]	2	2	2	1
Psychiatric Disorders				
Insomnia[9]	8	10	9	5
Agitation[10]	3	3	3	1
Renal and Urinary Disorders				
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

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PrLYRICA® PREGABALIN

PRESCRIBING SUMMARY

PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION: Analgesic Agent

INDICATIONS AND CLINICAL USE

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

LYRICA is indicated for the management of pain associated with fibromyalgia 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

Angioedema

There have been post-marketing reports of angioedema in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), neck, throat, and larynx/upper airway. There have been reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Some of these patients did not have reported previous history/episode(s) of angioedema. LYRICA should be immediately discontinued in patients with these symptoms. During the pre-marketing assessment of pregabalin in clinical trials, angioedema was reported as a rare reaction (see Product Monograph, ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions and Post-Marketing Adverse Drug Reactions).

Caution should be exercised when prescribing LYRICA to patients with previous history/episode(s) of angioedema and related events. In addition, patients who are taking other drugs associated with angioedema (eg, ACE-inhibitors) may be at increased risk of developing this condition.

Hypersensitivity

There have been post-marketing reports of hypersensitivity reactions (e.g. skin redness, blisters, hives, rash, dyspnea, and wheezing). Pregabalin should be discontinued immediately if such symptoms occur (see Product Monograph, Post-Marketing Adverse Drug Reactions).

Renal Failure

In both clinical trials of various indications and post-marketing database, there are reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Caution is advised when prescribing pregabalin to the elderly or those with any degree of renal impairment (see Product Monograph, Special Populations, *Renal;* Abrupt or Rapid Discontinuation; ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions; and DOSAGE AND ADMINISTRATION).

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: LYRICA may cause peripheral edema. In controlled clinical trials, pregabalin treatment caused peripheral edema in 6% of patients compared with 2% of patients in the placebo group. In these studies, 0.5% of pregabalin patients and 0.2% 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 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). Although this adverse reaction has mostly been observed in elderly cardiovascular-compromised patients during pregabalin treatment for a neuropathic pain indication, some cases have occurred in patients without reported edema or previous history of cardiovascular disease. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Weight Gain: LYRICA may cause weight gain. In pregabalin-controlled clinical trials with durations of up to 14 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 (0.4%) 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.

Pregabalin-associated weight gain did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema and was not necessarily due to edema-related events (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: LYRICA may cause dizziness and somnolence. In controlled studies, pregabalin caused dizziness in 31% of patients compared to 9% in placebo. Somnolence was experienced by 22% and 7% 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. In these studies, dizziness and somnolence led to withdrawal of 5% (placebo: 0.6%) and 3% (placebo: 0.3%) of the pregabalin-treated patients, respectively.

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

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trial Adverse Drug Reactions: *Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of 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.

Most Common Adverse Events in Controlled Clinical Studies in Fibromyalgia: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness (37.5%), somnolence (18.6%), weight gain (10.6%), dry mouth (7.9%), blurred vision (6.7%), peripheral edema (6.1%), constipation (5.8%), and disturbance in attention (5.3%). 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 some elderly patients and those 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 twice a day, 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 (see Product Monograph, ADVERSE REACTIONS, Tables 1 and 5). Doses above 600 mg/day have not been studied and are not recommended.

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. Doses above 600 mg/day have not been studied and are not recommended.

Pain associated with fibromyalgia: The recommended dosage is 300 to 450 mg/day, given in two divided doses. 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. Based on individual response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg BID (450 mg/day). In some patients, efficacy of LYRICA has been demonstrated within the first 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 twice a day, BID) can be used. However, in clinical trials of fibromyalgia, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced significantly higher rates of adverse events and discontinued the trial more frequently (see Product Monograph, ADVERSE REACTIONS, Tables 7 and 10). In view of the dose-related adverse events, the decision to treat patients with doses above 450 mg/day should be based on clinical judgment of the treating physician. Doses above 600 mg/day have not been studied and are not recommended.

Administration: LYRICA is given orally with or without food.

Supplemental Product Information

Special Populations: *Renal:* There have been reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin showed reversibility of this event in some cases (see Product Monograph, WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions; and DOSAGE AND ADMINISTRATION). Because pregabalin is eliminated primarily by renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients or those with renal impairment (see Product Monograph, ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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.

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	up to		Maximum daily dose	
≥60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
<15	25	25-50	50-75	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 50-75 mg QD regimen: take one supplemental dose of 75 mg or 100 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. In post-marketing experience, the most commonly reported adverse events observed when pregabalin was taken in overdose (dose range from 800 mg/day up to 11,500 mg as a single dose) included affective disorder, somnolence, confusional state, depression, agitation, and restlessness.

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.

Working together for a healthier world™

See our AD on page A-6&A-7

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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*

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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

Adverse Experience		Copaxone® (n=125) N	Copaxone® (n=125) %	Placebo (n=126) N	Placebo (n=126) %
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
Nervous System	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.

See our AD on page A-3

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PrCATENA®

idebenone 150mg oral tablets

Prescribing Summary

CATENA,® indicated for the treatment of Friedreich's Ataxia, has been issued market authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the market authorization granted.

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: ATP Production Modulator

NOC/c INDICATIONS AND CLINICAL USE:

CATENA® may be useful in the symptomatic management of patients with Friedreich's Ataxia.

The clinical trial data supporting this conditional approval was based on patients ranging in age between 9 to 18 years.

Geriatrics (>65 years of age): The safety and efficacy of CATENA® in Friedreich's Ataxia has not been studied in patients >65 years. Therefore, caution should be exercised if the elderly are to be treated with CATENA.®

Pediatrics (<8 years of age): The safety and efficacy of CATENA® in Friedreich's Ataxia has not been studied in children under the age of 8 years. Therefore, caution should be exercised if this patient population is to be treated with CATENA.®

NOC/c CONTRAINDICATIONS:

CATENA® is contraindicated in patients:

- who are hypersensitive to idebenone or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING);
- who have moderate or severe hepatic impairment;
- who have severe renal impairment.

Safety Information

NOC/c WARNINGS AND PRECAUTIONS

Hematologic Leucocytopenia and agranulocytosis have been reported on rare occasions from the postmarketing use of idebenone.

A complete blood cell count (CBC) should be performed prior to initiation of therapy, and regularly thereafter (see Monitoring and Laboratory Tests). Patients should be instructed to consult their physician at any time if: they have a cold or flu-like symptoms or symptoms suggestive of another infectious disease; if they feel particularly lacking in energy; or if they bruise or bleed more readily or longer than usual. The physician should then assess the necessity of performing a CBC.

Hepatic/Biliary/Pancreatic CATENA® should not be prescribed to patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS). Caution should be exercised when prescribing to patients with mild hepatic impairment.

Studies in patients with mild hepatic impairment have shown increased plasma concentrations of inactive metabolites of idebenone. The clinical significance of this finding is unknown. Blood/liver monitoring should be performed prior to initiation of therapy and regularly thereafter (see Monitoring and Laboratory Tests).

Patients should be advised to consult their physician if they experience signs of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms).

Renal Studies in patients with moderate renal impairment have shown increased plasma concentrations of inactive metabolites of idebenone. The clinical significance of this finding is unknown. Caution should be exercised when prescribing to patients with mild to moderate renal impairment.

Special Populations

Pregnant Women: CATENA® has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

However, as the potential risk is unknown, use of CATENA® during pregnancy is not recommended.

Nursing Women: It is not known whether idebenone is excreted in human breast milk. Breastfeeding is not recommended during treatment with CATENA.®

NOC/c WARNINGS AND PRECAUTIONS

Monitoring and Laboratory Tests

Complete Blood Cell Count: Patients should have a normal complete blood cell count (CBC) before initiating therapy with CATENA.® The CBC should be repeated 1 month after initiating therapy with CATENA® or after increasing the dose, and then at 3 months, at 6 months and every 6 months thereafter. If, at any time, clinical symptoms justify, additional CBC should be performed. In the case of a low blood cell count, dose decrease or treatment discontinuation should be considered.

Liver Function Tests: Increases in liver function test values have been reported occasionally. Liver function tests should be performed 1 month after initiating therapy with CATENA® or after increasing the dose, and then at 3 months, at 6 months and every 6 months thereafter, as for CBC.

The frequency of additional liver function tests will depend on clinical judgement and relevant symptomatology.

Lactose Intolerance Lactose is a nonmedicinal ingredient in CATENA.® Patients with rare hereditary disease of galactose intolerance (galactosemia, glucose-galactose malabsorption or Lapp lactase deficiency) should not take this medicine.

CATENA® contains the colouring agent FD&C yellow No. 6 aluminium lake (CI 15985). It is also known as tartrazine. In some people, it may cause allergic reactions.

No Information to Report: General, Cardiovascular, Dependence/ Tolerance, Ear/Nose/Throat, Endocrine and Metabolism, Gastrointestinal, Genitourinary, Immune, Neurologic, Ophthalmologic, Perioperative Considerations, Psychiatric, Respiratory, Sensitivity/ Resistance, Skin.

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of adverse events in Friedreich's Ataxia trials were mild (NCI-CTC Grade 1). Gastrointestinal disorders such as diarrhea, nausea and dyspepsia were the most commonly reported reactions. Cases of reduced blood cell counts and increases of liver function values have been reported rarely.

A full listing of adverse reactions in Friedreich's Ataxia trials is provided in the Supplemental Product Information section.

To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at: telephone 1-866-234-2345; fax 1-866-678-6789; or email cadrmp@hc-sc.gc.ca.

Studies in Other Patients: Several studies in Alzheimer's Disease patients have been performed. See Abnormal Hematologic and Clinical Chemistry Findings, below.

Abnormal Hematologic and Clinical Chemistry Findings

Friedreich's Ataxia: In the Phase I Friedreich's Ataxia studies, there were no significant changes in the hematology or clinical chemistry parameters. In the Phase II Friedreich's Ataxia study (NICOSIA), low white cell counts were reported both with active medication and placebo treatment during the study. Two (16.7%) events occurred on high dose (2250 mg/day or 1350 mg/day), 0 on mid dose (900 mg/day or 450 mg/day if body weight 45 kg or below), 2 (16.7%) on low dose (360 mg/day or 180 mg/day if body weight 45 kg or below) and 3 (27.3%) on placebo.

One case of hyperkalemia was reported as an adverse event in a patient receiving idebenone (2250 mg/day or 1350 mg/day) but the potassium level was normal upon rechecking at a local laboratory.

Alzheimer's Disease: In a number of Phase III studies of CATENA® in Alzheimer's disease, there was a low incidence overall of hematology and liver function test abnormalities reported as adverse events. CATENA® was used in doses of up to 1080 mg/day in these trials.

With the exception of three instances of hypokalemia and one of hyponatremia, no laboratory parameter abnormalities were reported as serious adverse events.

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Postmarket Adverse Drug Reactions To date, worldwide exposure to idebenone is estimated at approximately 400,000 patient-years. This use has been in patients with cognitive diseases, and mostly at doses in the range of 90 to 180 mg/day, considerably lower than the doses now recommended for Friedreich's Ataxia.

During this period of 20 years up to May 2007, a total of 64 serious adverse drug reactions (SADRs) from spontaneous reports and from the literature have been reported. This included 23 patients listed with blood cell abnormalities, mostly involving reduced cell counts of white cells, red cells or platelets, and 9 patients with abnormal liver function values. Rarely, there have been reports of chromaturia and increased BUN. Please refer to the Supplemental Information section for more information on Adverse Events and Drug Interactions.

Administration

NOC/c DOSAGE AND ADMINISTRATION

Initially, CATENA® should be prescribed only by physicians experienced in the diagnosis and management of Friedreich's Ataxia. If necessary, subsequent follow-up and continuing treatment of the patient may be undertaken by nonspecialized physicians, under the supervision of a specialist.

Dosing Considerations CATENA® has not been studied in children < 8 years old or in geriatrics > 65 years of age.

Food increases the bioavailability of idebenone. Therefore CATENA® should always be taken with food.

Recommended Standard Dose and Dosage Adjustment

CATENA® should be administered three times a day with food. The tablets should not be broken or chewed.

Lower Dose Therapy

Patients weighing 45 kg or under:	150 mg (one tablet) three times a day (total: 450 mg)
Patients weighing over 45 kg:	300 mg (two tablets) three times a day (total: 900 mg)

Higher Dose Therapy

Patients weighing 45 kg or under:	450 mg (three tablets) three times a day (total: 1350 mg)
Patients weighing over 45 kg:	750 mg (five tablets) three times a day (total: 2250 mg)

The decision to use a higher dose should be made by the treating physician based on clinical judgement. Patients should be started on and remain on the lower dose for at least 6 months and move to a higher dose based on observed clinical benefit and tolerability. The required blood (CBC) and liver function tests should be performed before and after dose increase (see Monitoring and Laboratory Tests). If no additional improvement/efficacy is observed after 6 months on the higher dose, patients should be returned to their lower dose.

Missed Dose If a dose is missed, the next tablet(s) should be taken as originally planned. Double doses should not be taken to make up for forgotten tablets.

Administration Tablets should be swallowed whole with water.

OVERDOSAGE

Adverse events as a result of an overdose have not been observed during clinical trials. Patients with Friedreich's Ataxia (children, adolescents and adults) receiving 60 mg/kg for 4 weeks or 75 mg/kg as a single dose tolerated the medication well. There is no specific antidote for idebenone. Supportive treatment should be given. For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CATENA® is supplied in high density polyethylene bottles containing 90, 180, 270 and 450 tablets. Each orange, round, biconvex, film-coated tablet contains 150 mg idebenone. The tablets are engraved with "150" on one side and with the "Santhera logo" on the other side. In addition, each tablet contains the following nonmedicinal ingredients: croscarmellose sodium lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, povidone K25, silicon dioxide, talc, titanium dioxide (CI 77891), FD&C yellow No. 6 aluminium lake (CI 15985).

STORAGE AND STABILITY

Store at 15°C–30°C.

Supplemental Product Information

NOC/c ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Studies in Patients with Friedreich's Ataxia

Two Phase I studies evaluated the safety of idebenone in patients aged ≥8 years with Friedreich's Ataxia. In total, 94 patients were included in these studies and received doses of up to 75 mg/kg/day for 1 day or 60 mg/kg/day for 30 days.

A 6-month Phase II placebo-controlled study (NICOSIA) in Friedreich's Ataxia was designed to generate additional safety data on high-dose idebenone and to determine the efficacy of idebenone at three dose levels, up to a maximum of 2250 mg/day. Forty-eight (48) patients between 9 and 18 years of age (mean age approximately 14 years) were randomized. Adverse events were generally mild, and none led to discontinuation of study medication. Table 1 shows the events judged to be reactions to medication in the study.

Table 1: Number of patients with treatment-emergent adverse reactions in the NICOSIA study

Low dose = 360 mg/day (or 180 mg/day for patients weighing 45 kg or under)
Mid dose = 900 mg/day (or 450 mg/day for patients weighing 45 kg or under)
High dose = 2250 mg/day (or 1350 mg/day patients weighing 45 kg or under)

	Placebo (n=11)	Low Dose (n=12)	Mid Dose (n=13)	High Dose (n=12)
Any Body System	**5**	**9**	**10**	**4**
Cardiac Disorders	**1**	**0**	**0**	**1**
Angina pectoris	1	0	0	1
Gastrointestinal Disorders	**4**	**6**	**8**	**1**
Abdominal pain upper	0	0	1	0
Constipation	0	1	0	0
Diarrhea	0	2	4	0
Dyspepsia	1	2	2	0
Nausea	3	2	3	1
Reflux esophagitis	0	0	1	0
Vomiting	1	1	1	0
Infections and Infestations	**1**	**1**	**0**	**0**
Gastroenteritis	0	1	0	0
Influenza	1	0	0	0
Investigations	**0**	**0**	**0**	**1**
White blood cell count decreased	0	0	0	1
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**2**	**0**
Musculoskeletal chest pain	0	0	1	0
Myalgia	0	0	1	0
Nervous System Disorders	**1**	**4**	**3**	**4**
Disturbance in attention	0	0	1	0
Headache	1	3	2	4
Syncope	0	1	0	0
Psychiatric Disorders	**0**	**1**	**0**	**0**
Insomnia	0	1	0	0
Renal and Urinary Disorders	**0**	**0**	**1**	**0**
Chromaturia	0	0	1	0
Respiratory, Thoracic and Mediastinal Disorders	**1**	**0**	**0**	**0**
Dyspnea	1	0	0	0

DRUG INTERACTIONS

Overview

Idebenone competitively inhibits cytochrome P450 2C19 *in vitro*, with an IC_{50} of 2.3 µM. For all other isoenzymes tested, idebenone had higher IC_{50} values.

Drug-Drug Interactions

The major metabolizing enzyme of idebenone has not been determined, but the major elimination pathway is likely through conjugation. Inhibitors and inducers of CYP2C19, CYP1A2 and CYP3A4 may affect the metabolism of idebenone. The clinical relevance is unknown.

No significant pharmacokinetic (PK) interactions were observed between single doses of amitriptyline (75 mg), fluvoxamine (100 mg) or lithium (2252 mg) and either a single dose of 120 mg idebenone or 120 mg t.i.d. No significant PK interaction was observed between donepezil (5 mg once daily) and idebenone 360 mg t.i.d [1080 mg]) for 14 days.

Drug-Food Interactions

A study has been performed to investigate the effect of fat-rich meals on the bioavailability of CATENA.® Food increases the bioavailability of CATENA® (see DOSAGE AND ADMINISTRATION). Therefore CATENA® should always be taken with food.

Drug-Herb Interactions

No studies have been conducted to investigate interactions between CATENA® and herbs.

Drug-Laboratory Interactions

No studies have been conducted to investigate interactions between CATENA® and laboratory tests.

Drug-Lifestyle Interactions

No studies have been conducted to investigate the effects of CATENA® on ability to drive and use machinery.

The full Product Monograph, prepared for health professionals, can be obtained by contacting the Canadian Importer, GMD Distributing Inc., at: 1-866-270-1733.
It is also available on the Health Canada website: www.hc-sc.gc.ca

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Switzerland

Canadian importer/distributor:
GMD Distributing Inc.
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santhera Pharmaceuticals

CATENA® idebenone 150mg oral tablets

See our AD on page OFC

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NOTES AND ANNOUNCEMENTS

ERRATUM

Please note an error occurred in the printing of character symbols in the below article in the CJNS May issue:

Susceptibility to Febrile Seizures: More Than Just a Faulty Thermostat!
Asuri N. Prasad, Shashi S. Seshia Can J Neurol Sci. 2009; 36: 277-279

Page 278 - 5th right hand paragraph should read:

Kang et al showed temperature dependent trafficking and/or accelerated endocytosis of heterozygous mutant $\alpha1\beta2\gamma2$ receptors containing $\gamma2$ subunit mutations associated with febrile seizures.[31] They suggest that febrile seizures may be produced by a temperature-induced dynamic reduction in the expression and recycling of mutant surface $GABA_A$ receptors in response to fever. Thus, molecular genetics is helping to not only define the clinical spectrum of febrile seizures and febrile seizure+ syndromes but is also providing insights into possible mechanisms determining susceptibility.

We apologize for this unfortunate error of omission and the online version has been amended.

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CANADIAN NEUROLOGICAL SCIENCES FEDERATION

FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA

CONGRESS SPONSORS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

§ 60 mg twice-daily dosing administration[1]

Member R&D PAAB

1-866-364-4043

Cymbalta® DELAYED RELEASE CAPSULES
duloxetine HCl
FOR DIABETIC PERIPHERAL NEUROPATHIC PAIN

Boehringer Ingelheim Lilly

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See prescribing summary on page A-13-16