INFORMATION FOR AUTHORS

Submition Process

The manuscript submission process is broken into a series of 5 screens that gather detailed information about your manuscript and allow you to upload the pertinent files.

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

Before submitting a manuscript, please gather the following information:
• All Authors First Names, Middle Names/Initials, Last Names
• Author affiliations/Institutions
• Departments
• Phone and Fax Numbers
• Street Addresses
• E-mail Addresses
• Title and Running Title (you may copy and paste these from your manuscript)
• Your TITLE MUST BE UNDER 80 CHARACTERS (including spaces)

Structured Abstract (unless a Review Article, then Unstructured)

File Formats
• Manuscript files in Word, WordPerfect, or Text formats
• Figures/Images in TIF, EPS, PDF, or JPG formats (must follow high resolution formats below)
• Tables in XLS or DOC formats
• Figure/File mode/ideal resolution/Minimum resolution
• Line Bitmap 1200 dpi(ideal) 600 dpi(min)
• Color photo CMYK 300 dpi(ideal) 200 dpi(min)
• Black and White photos Grayscale 300 dpi(ideal) 200 dpi(min)
• Line/halftone combination Grayscale 600 dpi(ideal) 200 dpi(min)

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

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

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Cover Letter

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 a Structured 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. Review articles should be accompanied by an Unstructured abstract of 150 words or less. Brief Communications (Case Reports) require no Abstract.

Acknowledgements

Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text. The SI system (systeme international d'unites) 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. Cite references in numerical order according to their position in the Reference list in the text.

List all authors when there are six or fewer; for seven or more, list only the first three and add "et al".

For pagination (e.g., 33-7, not 33-37).

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

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 go to: www.nlm.nih.gov/bsd/uniform_requirements.html

Examples of correct forms of reference:

Journals

Chapter in a book

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.
INFORMATION FOR AUTHORS
SUBMISSION PROCESS (continued)

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
Brief Communications are published on various topics and should be limited to approximately 9 - 12 double-spaced manuscript pages (3 - 4 Journal pages) and may include illustrations and tables. Brief Communications do not require an abstract.

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.

Critically Appraised Topics (CATs)
Current research in clinical neurosciences. Each CAT will appraise one or two recent research articles dealing with a particular topic. Meta-analyses and systematic reviews will also be considered if pertaining to evidence-based neurological/neurosurgical practice. A complete CAT is a one or 2 page summary that includes all of the following:
- A brief title that summarizes the conclusion reached about the article.
- Clinical Bottom Lines consisting of short statements summarizing the key "take-home" points. The clinical problem which cues the reader to the nature of the case. The clinical problem comes from real life dilemmas that are faced by clinicians. The clinical question includes the patient, intervention, comparator, and outcome.
- The search strategy - including search terms, search engines used, and the reasons why the article chosen is the best evidence for the clinical question.
- The evidence is described briefly including the type of study, patient population, and outcomes reported for the article reviewed.
- The data is usually presented in tabular form and highlights the clinically significant data such as number needed to treat, specificity, hazard ratios, etc.
- Comments are added regarding the quality of the study and any concerns which were identified by the critical appraisal process.
- The reference, the appraiser, the date appraised, and the date expired.
- Lastly, it will include a clinical comment from an "expert" on the particular topic.

Neuroimaging Highlights
Neuroimaging Highlights are selected by the Editor-in-Chief and Neuroimaging Highlight Editors on the basis of two factors. The first is high quality "state of the art" imaging of a novel and uncommon (or common with an uncommon twist) neurological or neurosurgical disorder. The second factor is the clinical novelty of the case.

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

Images should be of the highest quality, submitted electronically as a tif file at a minimum of 300 dpi and at a size large enough for the printed journal (i.e. not less than 3 1/2" wide).

Suitability for publication is judged by a Neuroimaging Highlight Editor, the Editor-in-Chief and up to one additional external referee.

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

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

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

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Starting
The manuscript submission process starts by pressing the "Submit Manuscript" link on your "Home" page. Please make sure you have gathered all the required manuscript information listed above BEFORE starting the submission process.
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 (e.g., 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 hemaniosarcoma 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 HbA1c).

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 anemia. 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.

Most Common Adverse Events in Controlled Clinical Studies in Diabetic Neuropathy: The most common treatment-related adverse events (>5% and twice the rate of that seen in placebo) across all pregabalin doses were: peripheral edema (6.1%), constipation (5.8%), and disturbance in attention (5.3%). Adverse events were usually mild to moderate in intensity. Supplementary Product Information.

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.

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.

Neuropathic 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 patient 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 judgement 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.

ADVERSE REACTIONS. Post-Marketing Adverse Drug Reactions; and DOSAGE AND ADMINISTRATION. Because pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in vivo, 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 as a reuptake inhibitor associated with drug abuse. As with all CNS active drugs, 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 behavior).

ADDITIONAL DOSAGE INFORMATION. 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 dosing 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

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Total Pregabalin Daily Dose (mg/day)*</th>
<th>Recommended Dose Escalation†</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>150</td>
<td>450</td>
<td>600</td>
</tr>
<tr>
<td>30-60</td>
<td>75</td>
<td>225</td>
<td>300</td>
</tr>
<tr>
<td>15-30</td>
<td>25-50</td>
<td>100-150</td>
<td>150</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25</td>
<td>50-75</td>
<td>75</td>
</tr>
</tbody>
</table>

Supplementary dosage following hemodialysis (mg)*

Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg
Patients on the 50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg
Patients on the 75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg

TD = Three divided doses; BD = Two divided doses; QD = Single daily dose.

* Based on individual patient response and tolerability.
† Based on individual patient response and tolerability.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdose 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 clinicallly 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, confusion, suicidal ideation, depression, agitation, and restlessess.

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. Urinary pH should be titrated to alkaline values (e.g., administration of sodium bicarbonate) if the patient's clinical status suggests the need for acid-base manipulation. Patients with a history of significant renal insufficiency may be at greater risk of the effects of overdose.

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.

Supplemental Product Information.

Special Populations: Renal: There have been reports of patients, with or without previous history, experiencing renal failure following administration of pregabalin. Dose escalation should be done in combination with other medications. Discontinuation of pregabalin showed reversibility of this event in some cases (see Product Monograph: WARNING 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 needed for elderly patients or those with renal impairment (see Product Monograph: ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Pregnancy: 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.

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THERAPEUTIC CLASSIFICATION: Migraine Therapy

INDICATIONS AND CLINICAL USE

RELPA (eletriptan hydrobromide) is indicated for the acute treatment of migraine with or without aura in adults. RELPA tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of RELPAX tablets have not been established for cluster headache.

CONTRAINDICATIONS

RELPA tablets are contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive eletriptan. Ischemic cardiac syndromes include, but are not restricted to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS AND PRECAUTIONS).

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

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

RELPA is contraindicated within 24 h of treatment with another 5-HT, agonist, an ergotamine-containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide. RELPA is also contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine; in patients with severe hepatic impairment; and in patients with known hypersensitivity to eletriptan or any of its inactive ingredients.

SPECIAL POPULATIONS

Pregnant women

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

Nursing women

Caution should be exercised when RELPA tablets are administered to nursing women.

Eletriptan is excreted in human breast milk (see Supplemental Product Information).

Pediatrics (<18 years of age)

Safety and effectiveness of RELPA tablets in pediatric patients have not been established; therefore, RELPA is not recommended for use in patients under 18 years of age. The efficacy of RELPA tablets (40 mg) in patients 11-17 was not established in a randomized, placebo-controlled trial of 274 adolescent migraineurs.

Geriatrics (>65 years of age)

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

WARNINGS AND PRECAUTIONS

General

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

CYP3A4 inhibitors

See CONTRAINDICATIONS above.

Cardiovascular

Risk of myocardial ischemia and/or infarction and other cardiovascular events: As with other triptans, eletriptan has been associated with transient pain or pressure sensation in the chest or throat. Because of the potential of 5-HT, agonists to cause coronary vasospasm, eletriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that eletriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male >40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease, or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest. As a result, during the cardiovascular evaluation, the patient’s medical history, electrocardiograph, or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, eletriptan should not be administered (see CONTRAINDICATIONS).

These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events, such as myocardial infarction or coronary ischemia have occurred in patients without evidence of underlying cardiovascular disease. For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the 1st dose of eletriptan take place in the setting of a physician’s office or similar medically staffed and equipped facility unless the patient has previously received eletriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining, on the 1st occasion of use, an electrocardiogram (ECG) during the interval immediately following administration of eletriptan, in patients with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

It is recommended that patients who are intermittent long-term users of 5-HT, agonists including eletriptan, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use eletriptan. If symptoms consistent with angina occur after the use of eletriptan, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to therapy with eletriptan.

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

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

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive RELPA. As with other 5-HT, agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with RELPA tablets in the precordium, throat and jaw. Events that are localized to the chest, throat, neck and jaw have not been associated with arrhythmias or ischemic ECG changes in clinical trials.

Because 5-HT, agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal’s variant angina before receiving
additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud’s syndrome, following the use of any 5-HT₁ agonist are candidates for further evaluation (see CONTRAINDICATIONS and Supplemental Product Information).

Cerebrovascular events and fatalities associated with 5-HT₁ agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT₁ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Increase in blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving other 5-HT₁ agonists with and without a history of hypertension. In clinical pharmacology studies, oral eletriptan (at doses of 60 mg or more) was shown to cause small transient dose-related increases in blood pressure, predominantly diastolic, consistent with its mechanism of action and with other 5-HT₁ agonists. The effect was more pronounced in renally impaired and elderly subjects. A single patient with hepatic cirrhosis received eletriptan 60 mg and experienced a blood pressure of 220/93 mmHg 5 h after dosing. The treatment-related event persisted for 7 h.

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

The effects of severe hepatic impairment on eletriptan metabolism were not evaluated. RELPAX tablets should not be given to patients with severe hepatic impairment. No dose adjustment is necessary in mild to moderate impairment (see ADMINISTRATION and Supplemental Product Information).

Neurologic: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT₁ agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the 1st dose of eletriptan.

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

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

Renal: There was no significant change in clearance observed in subjects with mild, moderate or severe renal impairment. In some of these patients, an elevation in blood pressure was observed (see ADMINISTRATION). Sensitivity/resistance: Hypersensitivity: Owing to the possibility of cross-reactive hypersensitivity reactions, RELPAX should not be used in patients having a history of hypersensitivity to chemically-related 5-HT₁ receptor agonists (see ADVERSE REACTIONS and Supplemental Product Information).

ADVERSE REACTIONS

Adverse drug reaction overview

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

Typical 5-HT₁ agonist adverse reactions

As with other 5-HT₁ agonists, RELPAX has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limbs.

Increases in blood pressure

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients and without a history of hypertension treated with other 5-HT₁ agonists. RELPAX is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

Clinical trial adverse drug reactions

Among 5,934 patients who treated a single migraine headache with RELPAX, 20, 40 or 80 mg tablets in short-term, placebo-controlled trials, the most common and dose-related adverse events (AEs) reported with treatment with RELPAX were asthenia (7.2%), nausea (7.9%), dizziness (6.7%) and somnolence (6.2%) (see Supplemental Product Information and Table 1 below). RELPAX tablets are generally well tolerated. Across all doses, most AEs were mild or transient. The frequency of AEs in clinical trials did not increase when up to 2 doses of RELPAX tablets were taken within 24 h. The incidence of AEs in controlled clinical trials was not affected by gender, age, or race of patients. AE frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis, (e.g., SSRIs, beta blockers, calcium channel blockers, tricyclic antidepressants), estrogen replacement therapy and oral contraceptives.

DRUG INTERACTIONS

Effects of other drugs on eletriptan

CYP3A4 inhibitors: See CONTRAINDICATIONS and Supplemental Product Information

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

Other 5-HT₁ agonists: See CONTRAINDICATIONS.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when co-administered with 5-HT₁, agonists. If concomitant treatment with eletriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug-food interactions

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

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

Administration

Dosing considerations

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

Recommended dose and dosage adjustment

Adult (19-85 years of age): In controlled clinical trials, single doses of 20 mg and 40 mg were effective for the acute treatment of migraine in adults. A greater proportion of patients had a response following a 40 mg dose than following a 20 mg dose. Individuals may vary in response to doses of RELPAX tablets.

When initiating treatment with RELPAX, a starting dose of 20 mg or 40 mg may be considered. Patients who do not obtain satisfactory efficacy after an initial trial of 20 mg may be effectively treated with 40 mg in subsequent migraine attacks. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

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

The maximum daily dose should not exceed 40 mg.

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

Patients receiving potent CYP3A4 inhibitors

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

Patients with hepatic impairment

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

Patients with renal impairment

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

Administration

RELPAX tablets should be swallowed whole with water.


Study References

Supplemental Product Information

PRECAUTIONS AND WARNINGS

Pregnant women

In laboratory toxicity studies in rats and rabbits, oral administration of eletriptan was associated with developmentally toxic doses that were, on a mg/m² basis, 6 to 12 times greater than the clinical maximum recommended daily dose (MRDD) of 80 mg. The following information is based on a marginal increase in maternal body weights at doses of 30 mg/kg in rabbits and 15 mg/kg in rats, and on adverse fetal effects and/or maternal deaths at doses in all three species that were 10 times the MRDD in rats, 5 times the MRDD in rabbits, and 2.5 times the MRDD in rats.

In reproductive toxicity studies in rats and rabbits, oral administration of eletriptan was associated with developmental toxicity (decreased in utero body weight gain, skeletal variations, and fetal body weight) at doses that were, on a mg/m² basis, 6 to 12 times greater than the clinical maximum recommended daily dose (MRDD) of 80 mg. These increases in maternal body weights, maternal deaths, and fetal body weights were increased at 100 mg/kg/d (approximately 12 times the MRDD on a mg/m² basis), with maternal deaths increased at 300 mg/kg/d (approximately 37 times the MRDD on a mg/m² basis). In the rabbit, skeletal variations were increased at 100 mg/kg/d (approximately 12 times the MRDD on a mg/m² basis), with fetal body weights increased at 300 mg/kg/d (approximately 37 times the MRDD on a mg/m² basis). Maternal deaths were increased at 1000 mg/kg/d (approximately 120 times the MRDD on a mg/m² basis), with skeletal variations increased at 3000 mg/kg/d (approximately 370 times the MRDD on a mg/m² basis). The no-effect dose for developmental effects was 15 mg/kg/d (approximately 1.2 times the MRDD on a mg/m² basis), with maternal deaths increased at 300 mg/kg/d (approximately 24 times the MRDD on a mg/m² basis). Maternal deaths were increased at 3000 mg/kg/d (approximately 240 times the MRDD on a mg/m² basis).

The increase in structural alterations occurred in the rat and rabbit at doses that, on a mg/m² basis, were 12 times greater than (rat) and 24 times greater than (rabbit) the clinical maximum recommended daily dose (MRDD) of 80 mg.

In human volunteers, the peak plasma eletriptan level has been measured in the range of 6 to 12 times the MRDD on a mg/m² basis, and the AUC (at 24 h) was measured in the range of 18 to 37 times the MRDD on a mg/m² basis. These levels were achieved at 100 mg doses of eletriptan, and were approximately 1 to 2 times the MRDD on a mg/m² basis.

In vitro studies in human liver microsomes have shown that eletriptan is metabolized by the CYP3A4 liver enzyme system. In human male liver microsomes, the CYP3A4 enzyme produced a ratio of 1 to 0.7 for the relative activities of the 2 stereoisomers, R- and S-eletriptan. In human female liver microsomes, the CYP3A4 enzyme produced a ratio of 1 to 0.9 for the relative activities of the 2 stereoisomers, R- and S-eletriptan. The CYP3A4 enzyme produced a ratio of 1 to 0.5 for the relative activities of the 2 stereoisomers, R- and S-eletriptan. The CYP3A4 enzyme produced a ratio of 1 to 0.3 for the relative activities of the 2 stereoisomers, R- and S-eletriptan.

Cardiac events

Changes indicative of ischemia. There was also 1 report of atrial fibrillation in a patient with a past history of atrial fibrillation.

A subject with a history of angina, hypertension and hypercholesterolemia, receiving intravenous eletriptan (CMI of 138 ng/mL equivalent to 32.4 micromol/L), experienced a non-ST change (7.5%) in the electrocardiogram, a 5-HT, agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in plasma aldosterone concentration, and a 7% increase in plasma renin activity. Additionally, there was a 7% increase in plasma renin activity and a 5% increase in plasma aldosterone concentration. The resulting eletriptan concentration-time profile was similar to that seen in the plasma over 24 h, with very low concentrations evident by minimally decreased maternal body weight gain during gestation.

Further, variability associated with AE reporting, the terminology used to describe AEs, etc., limit the value of the quantitative frequency data. Frequent AEs are those occurring in at least 1/100 patients, infrequent AEs occurring in at least 1/1000 patients. Rare AEs are those occurring in less than 1/1000 patients.

Properly designed, double-blind, placebo-controlled studies are the only way to establish the true frequency of adverse effects and to adequately evaluate the importance and potential significance of rarely occurring events. Further, variability associated with AE reporting, the terminology used to describe AEs, etc., limit the value of the quantitative frequency data. Frequent AEs are those occurring in at least 1/100 patients, infrequent AEs occurring in at least 1/1000 patients. Rare AEs are those occurring in less than 1/1000 patients.

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**DRUG INTERACTIONS**

**CYP3A4 inhibitors:** A clinical study demonstrated about a 3-fold increase in \( C_{\text{max}} \) and about a 4-fold increase in AUC of eletriptan when co-administered with ketoconazole. The half-life of eletriptan increased from 2.8 h to 5.4 h.

**Erythromycin:** A clinical study demonstrated about a 3-fold increase in \( C_{\text{max}} \) and about a 6-fold increase in the AUC of eletriptan when co-administered with erythromycin.

**Fluconazole:** Co-administration of fluconazole and eletriptan yields about a 14-fold increase in \( C_{\text{max}} \) and about a 2-fold increase in AUC of eletriptan.

**Ketoconazole:** It has also been shown that co-administration of ketoconazole and eletriptan yields about a 2-fold increase in \( C_{\text{max}} \) and about a 3-fold increase in AUC of eletriptan.

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

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

**The effect of eletriptan on other drugs**

The effect of eletriptan on other drugs is generally minimal. However, as with all drugs, it is important to be aware of potential drug interactions. The following interactions have been reported:

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2011 Clinical Fellowship in Neuromuscular Disease

The Montreal Neurological Institute and the Department of Neurology and Neurosurgery at McGill University are seeking highly qualified candidates for the "Talecris Clinical Fellowship in Neuromuscular Disease", sponsored by Talecris Biotherapeutics. Candidates must have completed residency training in neurology and should have an interest in developing and academic career specializing in neuromuscular diseases. Canadian and American trained neurologists are encouraged to apply.

This 2-year fellowship, starting in July 2011, will provide opportunities for advanced clinical and research training in areas related to neuromuscular diseases. The main clinical activities will focus on patients seen in our neuropathy, neuromuscular, and myasthenia gravis clinics at the Montreal Neurological and the Montreal General Hospitals, where the fellow will be exposed to a diverse range of disorders of peripheral nerve, muscle, and neuromuscular junction. In addition, there are weekly sessions for interpretation and reporting of nerve and muscle biopsies.

The Fellow will also receive research training in basic or clinical research. The details of this part of the program will be arranged in consultation with the program directors. However, the fellow will be expected to develop a research project that will lead to publications and presentations at international meetings. To accomplish this he/she will have access to a large group of outstanding basic and clinical scientists at the Montreal Neurological Institute, the Montreal General Hospital (Centre for Research in Neuroscience), and McGill University whose research relates to neuromuscular disease. This group includes Drs S. Carbonetto, S. David, H. Durham, K. Hastings, P. Holland, P. Maghighi, J. Nalbantoglu, E. Shoubridge, and T. Taivassalo.

The Montreal Neurological Institute and Hospital are on the McGill University campus in downtown Montreal, and the Montreal General Hospital is near by. Montreal is one of North America’s most lively and affordable cities with an outstanding quality of life.

Candidates should send a copy of their CV, a letter outlining their career goals and three reference letters to Dr. Colin Chalk (colin.chalk@mcgill.ca).
The Canadian Neurological Sciences Federation is pleased to recognize those Sponsors who have already committed to supporting the 2010 Congress. These organizations partner with CNSF to determine the causes of, and develop treatment for diseases and injuries of the nervous system, and in the care of patients with these diseases and injuries. Along with support of the Canadian Journal of Neurological Sciences and other initiatives the CNSF maintains throughout the year, these organizations graciously provided educational grants to the Annual Congress, this year in Quebec City, Quebec, June 8-11, 2010.
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