INFORMATION FOR AUTHORS
SUBMISSION PROCESS

Submission 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.

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

Cover Letter

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

1. Rose ME, Huerbin MB, Melick J, 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

1. 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.

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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 Communciations 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 Communciations 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.

Permissions and Releases

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

Conflict of Interest

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

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

Getting Help

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

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

Logging into the system with your password

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

Clicking on the "Check Status" link at the bottom of the displayed page

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

Starting

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

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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

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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.

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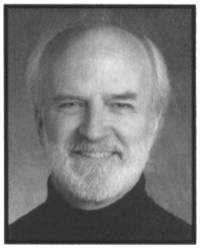

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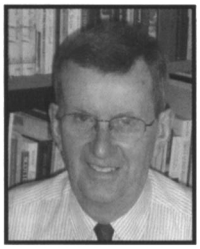

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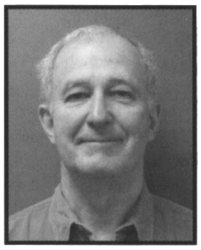

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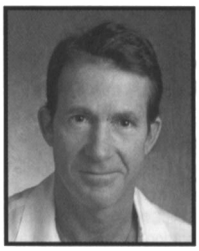

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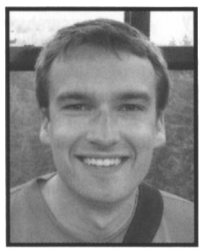

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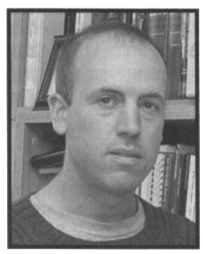

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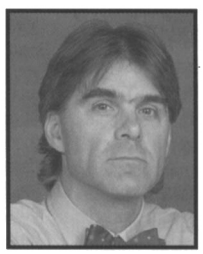

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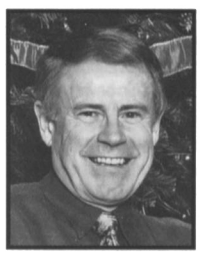

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Legend:
CNSF - *Canadian Neurological Sciences Federation;* NSFC - *Neurological Sciences Foundation of Canada;* CNS - *Canadian Neurological Society;*
CNSS - *Canadian Neurosurgical Society;* CSCN - *Canadian Society of Clinical Neurophysiologists;*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

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Maxalt®

rizatriptan benzoate tablets

Maxalt RPD®

rizatriptan benzoate wafers

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: 5-HT_1 Receptor Agonist

INDICATIONS AND CLINICAL USE

Adults

MAXALT® is indicated for acute treatment of migraine attacks with or without aura in adults. MAXALT® is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS in the Supplemental Product Information section). Safety and effectiveness of MAXALT® have not been established for cluster headache, which is present in an older, predominantly male population.

Pediatrics (<18 years of age)

The safety and efficacy of MAXALT® has not been established in patients under 18 years of age and its use in this age group is not recommended (see WARNINGS AND PRECAUTIONS).

Geriatrics (>65 years of age)

The safety and effectiveness of MAXALT® has not been adequately studied in individuals over 65 years of age. Its use in this age group is, therefore, not recommended (see WARNINGS AND PRECAUTIONS).

Special Populations and Conditions

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

CONTRAINDICATIONS

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

Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS AND PRECAUTIONS).

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

MAXALT® is contraindicated within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

MAXALT® is contraindicated in patients with hemiplegic, ophthalmoplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see Drug Interactions).

Because there are no data available, MAXALT® is contraindicated in patients with severe hepatic impairment.

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

Safety Information

WARNINGS AND PRECAUTIONS

General

MAXALT® should only be used where a clear diagnosis of migraine has been established.

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Psychomotor Effect

Dizziness, somnolence and asthenia/fatigue were experienced by some patients in clinical trials with MAXALT® (see ADVERSE EVENTS). Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that MAXALT® does not adversely affect them.

Cardiovascular

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

MAXALT® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT_1 agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of other 5-HT_1 agonists, and may therefore also occur with MAXALT®. Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT® should not be given to patients *with documented ischemic or vasospastic coronary* artery disease (see CONTRAINDICATIONS). It is strongly recommended that MAXALT® not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, MAXALT® should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of rizatriptan should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT®, in these patients with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

Intermittent long-term users of MAXALT® who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluation as they continue to use MAXALT®.

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

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

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of rizatriptan. Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following MAXALT® administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS).

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists

MAXALT® may cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience with MAXALT®

Among the approximately 4200 patients who were treated with at least a single oral dose of either 5 or 10 mg rizatriptan in premarketing clinical trials of MAXALT®, electrocardiac adverse experiences were observed in 33 patients. One patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

Postmarketing Experience with MAXALT®

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

Cerebrovascular Events and Fatalities Associated with 5-HT_1 Agonists

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported *in patients treated with 5-HT_1 agonists; and some have* resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with MAXALT® in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude *other potentially serious neurological conditions. If a patient* does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Special Cardiovascular Pharmacology Studies with Another 5-HT_1 Agonist

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

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperemic myocardial blood flow

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(~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT_1 agonist is not known.

Similar studies have not been done with MAXALT®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Other Vasospasm-Related Events

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive postmarket experience has shown the use of another 5-HT_1 agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT® (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. Rizatriptan is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, MAXALT® should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

Endocrine and Metabolism

Phenylketonurics

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

Hepatic/Biliary/Pancreatic

Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph and DOSAGE AND ADMINISTRATION). Since there are no data in patients with severe hepatic impairment, rizatriptan is contraindicated in this population (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as MAXALT®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, MAXALT® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists.

Neurologic

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headache that were subsequently shown to have been secondary to an evolving neurological lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of MAXALT®.

Seizures

Caution should be observed if MAXALT® is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold. There have been very rare reports of seizures following administration of MAXALT® in patients with or without risk factors or previous history of seizures (see ADVERSE REACTIONS, Post-Marketing Adverse Reactions, Nervous System in the Supplemental Product Information).

Ophthalmologic

Binding to Melanin-Containing Tissues

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin-rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one-year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Renal

Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan, resulting in approximately 44% increase in plasma concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph, and DOSAGE AND ADMINISTRATION).

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with MAXALT® and SSRIs (e.g., sertraline, escitalopram oxalate, and fluoxetine) or SNRIs (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see DRUG INTERACTIONS).

Special Populations and Conditions

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

ADVERSE REACTIONS

(see Supplemental Product Information for full listing)

Adverse Drug Reaction Overview

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

Long-Term Safety

In long-term extension studies, a total of 1854 patients treated 16,150 migraine attacks with MAXALT® 5 mg Tablets and 24,043 attacks with MAXALT® 10 mg Tablets over a period of up to 1 year. In general, the types of clinical adverse experiences observed in the extension studies were similar to those observed in the acute studies. However, the incidences of most clinical adverse events were approximately 3-fold higher in extension, as expected, based on increased observation time. The most common adverse events per attack (defined as occurring at an incidence of at least 1%) for MAXALT® 5 mg and 10 mg, respectively, were as follows: nausea (3%, 4%), dizziness (2%, 2%), somnolence 2%, 4%), asthenia/fatigue (2%, 2%), headache (1%, 2%), vomiting (1%, <1%), chest pain (<1%, 1%) and paresthesia (<1%, 2%). Due to the lack of placebo controls in the extension studies, the role of MAXALT® in causation cannot be reliably determined.

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

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

DRUG INTERACTIONS

Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Monoamine Oxidase Inhibitors

Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). In a drug interaction study, when MAXALT® 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, *reversible MAO-A inhibitor, moclobemide 150 mg t.i.d.*, there were mean increases in rizatriptan AUC and C_{max} of 119% and 41%, respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. Drug interaction studies were not conducted with selective MAO-B inhibitors.

The specificity of MAO-B inhibitors diminishes with higher doses and varies among patients. Therefore, co-administration of rizatriptan in patients taking MAO-A or MAO-B inhibitors is contraindicated (see CONTRAINDICATIONS).

Nadolol/Metoprolol

In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Oral Contraceptives

In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT® (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Other 5-HT_1 Agonists

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

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

Propranolol

MAXALT® should be used with caution in patients receiving propranolol, since the pharmacokinetic behavior of rizatriptan during co-administration with propranolol may be unpredictable. In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC and C_{max} for rizatriptan were increased by 70% and 75%, respectively, during propranolol administration. In one subject, a 4-fold increase in AUC and 5-fold increase in C_{max} was observed. This subject was not distinguishable from the others based on demographic characteristics. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol (see DOSAGE AND ADMINISTRATION).

Selective Serotonin Reuptake Inhibitors / Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported in post-marketing experience during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see WARNINGS AND PRECAUTIONS).

In a pharmacokinetic study with paroxetine and rizatriptan, paroxetine had no influence on the plasma levels of rizatriptan.

Food

Interactions with food have not been studied. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT® was administered without regard to food.

Administration

DOSAGE AND ADMINISTRATION

(see Product Monograph for complete information)

Dosing Considerations

MAXALT® is recommended only for the acute treatment of migraine attacks. MAXALT® should not be used prophylactically. Controlled trials have not established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Recommended Dose and Dosage Adjustment

ADULTS

MAXALT® Tablets and MAXALT RPD® Wafers

The recommended single adult dose is 5 mg. The maximum recommended single dose is 10 mg. There is evidence that the 10 mg dose may provide a greater effect than the 5 mg dose (see CLINICAL TRIALS in the Product Monograph). The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10 mg dose with the potential risk for increased adverse events.

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

Redosing

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

Patients receiving propranolol

A single 5 mg dose of MAXALT® should be used. In no instances should the total daily dose exceed 10 mg per day, given in two doses, separated by at least two hours (see DRUG INTERACTIONS).

Renal Impairment

In hemodialysis patients with severe renal impairment (creatinine clearance <2 mL/min/1.73 m^2), the AUC of rizatriptan was approximately 44% greater than in patients with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph). Consequently, if treatment is deemed advisable in these patients, the 5 mg MAXALT® Tablet or Wafer should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in renally impaired patients has not been evaluated.

Hepatic Impairment

MAXALT® is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) due to the absence of safety data. Plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the Product Monograph). Consequently, if treatment is deemed advisable in the presence of moderate hepatic impairment, the 5 mg MAXALT® Tablet or Wafer should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in hepatically impaired patients has not been evaluated.

Patients with Hypertension

MAXALT® should not be used in patients with uncontrolled or severe hypertension. In patients with mild to moderate controlled hypertension, patients should be treated cautiously at the lowest effective dose.

OVERDOSAGE

No overdoses of MAXALT® were reported during clinical trials.

Rizatriptan 40 mg (administered as either a single dose or as two doses with a 2-hour interdose interval) was generally well tolerated in over 300 patients; dizziness and somnolence were the most common drug-related adverse effects.

In a clinical pharmacology study in which 12 subjects received rizatriptan, at total cumulative doses of 80 mg (given within four hours), two subjects experienced syncope and/or bradycardia. One subject, a female aged 29 years, developed vomiting, bradycardia, and dizziness beginning three hours after receiving a total of 80 mg rizatriptan (administered over two hours); a third degree AV block, responsive to atropine, was observed an hour after the onset of the other symptoms. The second subject, a 25-year-old male, experienced transient dizziness, syncope, incontinence, and a 5-second systolic pause (on ECG monitor) immediately after a painful venipuncture. The venipuncture occurred two hours after the subject had received a total of 80 mg rizatriptan (administered over four hours).

In addition, based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT®. The elimination half-life of rizatriptan is 2 to 3 hours (see ACTION AND CLINICAL PHARMACOLOGY in the Product Monograph). Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

There is no specific antidote to rizatriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Special Populations and Conditions

Pregnant Women: In a reproduction study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation. These effects occurred in the absence of any apparent maternal toxicity (maternal plasma drug exposures were 22 and 337 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 20 mg). The developmental no-effect dose was equivalent to 2.25 times human exposure at the MRDD.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses at the equivalent of 337 times and 168 times, respectively, the human MRDD, during organogenesis. However, fetal weights were decreased in conjunction with decreased maternal weight gain at these same doses. The developmental no-effect dose in both rats and rabbits was 22 times the human MRDD. Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Impairment of Fertility

In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with an equivalent of 337 times the maximum recommended daily dose (MRDD) of 20 mg in humans. The no-effect dose was 22 times the MRDD. There was no impairment of fertility or reproductive performance in male rats treated with up to 825 times the MRDD.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MAXALT® is administered to women who are breast-feeding. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

Pediatrics (< 18 years of age): MAXALT® is not recommended for use in patients under 18 years of age. In a randomized placebo-controlled trial of 291 adolescent migraineurs, aged 12-17 years, the efficacy of MAXALT® Tablets (5 mg) was not different from that of placebo (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions in the product monograph).

Geriatrics (> 65 years of age): The safety and effectiveness of MAXALT® has not been adequately studied in individuals over 65 years of age. The risk of adverse reactions to this drug may be greater in elderly patients, as they are more likely to have decreased hepatic function, be at higher risk for CAD, and experience blood pressure increases that may be more pronounced. Clinical studies with MAXALT® did not include a substantial number of patients over 65 years of age (n=17). Its use in this age group is, therefore, not recommended.

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

Monitoring and Laboratory Tests

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

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.

Experience in Controlled Clinical Trials with MAXALT®

Typical 5-HT_1 Agonist Adverse Reactions

As with other 5-HT_1 agonists, MAXALT® has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety

Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of MAXALT® Tablets. The most common adverse events during treatment with MAXALT® were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose-related. In long-term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

Tables 1 and 2 list the adverse events regardless of drug relationship (incidence ≥ 1% and greater than placebo) after a single dose of MAXALT® Tablets and MAXALT RPD® Wafers, respectively. Most of the adverse events appear to be dose-related. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 1
Incidence (≥ 1% and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT® Tablets or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials†

	% of Patients		
	Placebo	MAXALT® 5 mg	MAXALT® 10 mg
Number of Patients	627	977	1167
Symptoms of Potentially Cardiac Origin			
Upper Limb Sensations*	1.3	1.7	1.8
Chest Sensations*	1.0	1.6	3.1
Neck/Throat/Jaw Sensations*	0.6	1.4	2.5
Palpitations	0.2	0.9	1.0
Body as a Whole			
Asthenia/Fatigue	2.1	4.2	6.9
Abdominal Pain	1.0	1.7	2.2
Digestive System			
Nausea	3.5	4.1	5.7
Dry Mouth	1.3	2.6	3.0
Vomiting	2.1	1.6	2.3
Nervous System			
Dizziness	4.5	4.2	8.9
Somnolence	3.5	4.2	8.4
Headache	0.8	1.8	2.1
Paresthesia	1.0	1.5	2.9
Tremor	1.0	1.3	0.3
Insomnia	0.3	1.0	0.3
Skin and Skin Appendage			
Flushing	1.0	0.6	1.1

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

†Data from Studies 022, 025, 029 and 030.

Table 2
Incidence (≥ 1% and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT RPD® Wafers or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials†

	% of Patients		
	Placebo	MAXALT RPD® 5 mg	MAXALT RPD® 10 mg
Number of Patients	283	282	302
Symptoms of Potentially Cardiac Origin			
Chest Sensations*	0.4	1.4	1.7
Neck/throat/Jaw Sensations*	0.4	1.4	2.0
Tachycardia	1.1	1.4	0.3
Upper Limb Sensations*	0.4	0.7	2.0
Palpitations	0.4	0.4	1.0
Body as a Whole			
Asthenia/Fatigue	0.4	2.1	3.6
Digestive System			
Dry Mouth	2.1	6.4	6.0
Nausea	5.7	6.4	7.0
Dyspepsia	0.7	1.1	2.0
Acid Regurgitation	0	1.1	0.7
Salivation Increase	0	0	1.3
Musculoskeletal System			
Regional Heaviness	0	0	1.0
Nervous System			
Dizziness	3.9	6.4	8.6
Somnolence	2.8	4.3	5.3
Headache	0.7	1.8	2.0
Insomnia	0	1.4	0.7
Paresthesia	0.4	1.4	3.0
Hypesthesia	0	1.4	0.7
Mental Acuity Decreased	0	1.1	0.3
Tremor	0.7	1.1	0
Nervousness	0.4	1.1	0.7
Respiratory System			
Pharyngeal Discomfort	0	1.1	0.7
Skin and Skin Appendage			
Sweating	0.7	1.1	1.0
Special Senses			
Taste Perversion	1.1	1.4	2.3
Blurred Vision	0	0.4	1.3

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

†Data from Studies 039 and 049.

MAXALT® was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. The incidences of adverse experiences were not affected by age, gender or use of prophylactic medications. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association with the Administration of MAXALT®

In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of MAXALT® in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used MAXALT® 5 mg and 10 mg tablets in Phase II and III studies (n=3716) and reported an event divided by the total number of patients exposed to MAXALT®. All reported events are included, except those

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already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those defined as those occurring in at least 1/100 patients; infrequent adverse experiences are those occurring in 1/100 to 1/1000 patients; and rare adverse experiences are those occurring in fewer than 1/1000 patients.

Body as a Whole

Frequent were warm sensations, chest pain and chills/cold sensations. Infrequent were heat sensitivity, facial edema, hangover effect, abdominal distention, edema/swelling and malaise. Rare were fever, orthostatic effects, and syncope.

Cardiovascular

Frequent was palpitation. Infrequent were tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. Rare were angina pectoris and blood pressure increased.

Digestive

Frequent was diarrhea. Infrequent were dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. Rare were anorexia, appetite increase, gastritis, paralysis (tongue), eructation and glosodynia.

Metabolic

Infrequent was dehydration.

Musculoskeletal

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

Neurological/Psychiatric

Frequent were hypesthesia and mental acuity decreased. Infrequent were nervousness, vertigo, insomnia, anxiety, depression, euphoria, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation, hyperesthesia, sleep disorder, speech disorder, migraine and spasm. Rare were dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory

Frequent were dyspnea and pharyngeal discomfort. Infrequent were pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion, dry nose, epistaxis, and sinus disorder. Rare were cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses

Frequent was taste perversion. Infrequent were blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. Rare were hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage

Infrequent were sweating, pruritus, rash, and urticaria. Rare were erythema, acne, and photosensitivity.

Urogenital System

Frequent was hot flashes. Infrequent were urinary frequency, polyuria, and menstruation disorder. Rare was dysuria.

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

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported very rarely and most have been reported in patients with risk factors predictive of CAD: Myocardial ischemia or infarction, cerebrovascular accident.

The following adverse reactions have also been reported:

Hypersensitivity: Hypersensitivity reaction, anaphylaxis/anaphylactoid reaction, angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, urticaria, rash, toxic epidermal necrolysis.

Nervous System: serotonin syndrome.

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

Musculoskeletal: facial pain.

Special Senses: Dysgeusia.

Vascular disorders: Peripheral vascular ischemia

Drug Abuse and Dependence

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

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

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Migraine Therapy

INDICATIONS AND CLINICAL USE

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

RELPAX tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see **CONTRAINDICATIONS**). Safety and effectiveness of **RELPAX** tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

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

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

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

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

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

SPECIAL POPULATIONS

Pregnant women

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

Nursing women

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

Pediatrics (<18 years of age)

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

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

Geriatrics (>65 years of age)

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

Safety Information

WARNINGS AND PRECAUTIONS

General

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

CYP3A4 inhibitors

See CONTRAINDICATIONS above.

Cardiovascular

Risk of myocardial ischemia and/or infarction and other cardiac events: As with other triptans, eletriptan has been associated with transient pain or pressure sensation in the chest or throat. Because of the potential of 5-HT$_1$ agonists to cause coronary vasospasm, eletriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that eletriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male >40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease, or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, eletriptan should not be administered (see CONTRAINDICATIONS).

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

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

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

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

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

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

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

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

Because 5-HT$_1$ agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving

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additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome, following the use of any 5-HT_1 agonist are candidates for further evaluation (see **CONTRAINDICATIONS** and **Supplemental Product Information**).

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

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

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

Hepatic

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

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

Neurologic

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the 1st dose of eletriptan.

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

Psychomotor effect

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

Renal

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

Sensitivity/resistance

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

ADVERSE REACTIONS

Adverse drug reaction overview

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

Typical 5-HT_1 agonist adverse reactions

As with other 5-HT_1 agonists, **RELPAX** has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limbs.

Increases in blood pressure

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. **RELPAX** is contraindicated in patients with uncontrolled hypertension (see **CONTRAINDICATIONS**).

Clinical trial adverse drug reactions

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

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

DRUG INTERACTIONS

Effects of other drugs on eletriptan

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

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

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

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

Drug-food interactions

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

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

Administration

Dosing considerations

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

Recommended dose and dosage adjustment

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

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

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

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

The maximum daily dose should not exceed 40 mg.

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

Patients receiving potent CYP3A4 inhibitors

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

Patients with hepatic impairment

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

Patients with renal impairment

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

Administration

RELPAX tablets should be swallowed whole with water.

Study References

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

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Pregnant women

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

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

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

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

Nursing women

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

Geriatrics (>65 years of age)

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

Cardiovascular

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

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

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

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

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

Special cardiovascular pharmacology studies with another 5-HT$_1$ agonist: In subjects (n=10) with suspected CAD undergoing angiography, a 5-HT$_1$ agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by 4 subjects. Clinically significant increases in blood pressure were experienced by 3 of the subjects (2 of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant CAD.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT$_1$ agonist is not known.

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

Dependence/tolerance

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

Hepatic

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

Ophthalmologic

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

Preclinical toxicology

Binding to melanin-containing tissues: In rats treated with a single intravenous (3 mg/kg) dose of radiolabelled eletriptan, elimination of radioactivity from the retina was prolonged, suggesting that eletriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin-rich tissues over time, this raises the possibility that eletriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with eletriptan in the 1-year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

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

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

Sensitivity/resistance

Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred in patients receiving other 5-HT$_1$ agonists. Such reactions can be life-threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see **ADVERSE REACTIONS**).

Sexual function/reproduction

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

ADVERSE REACTIONS

Clinical trial adverse drug reactions

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

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

Table 1 lists the most common AEs that occurred in the subset of 7,131 patients with migraine who received eletriptan doses of 20 mg, 40 mg, 80 mg or placebo in worldwide, placebo-controlled clinical trials. AEs that were more frequent in a **RELPAX** treatment group compared to the placebo group with an incidence >1% are included in Table 1. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, those frequency estimates may not apply, as the conditions of use, reporting behaviour, and the kinds of patients treated may differ.

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

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

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

Other events observed in association with the administration of RELPAX tablets

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

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

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

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

Endocrine: Rare: goiter, thyroid adenoma and thyroiditis.

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

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

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

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

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

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

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

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

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

Gastro-intestinal disorders: Ischaemic colitis;

Nervous system disorders: Syncope;

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

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

DRUG INTERACTIONS

Effects of other drugs on eletriptan

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

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

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

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

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

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

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

The effect of eletriptan on other drugs

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

Drug-herb interactions

Interactions with herbal products have not been established.

Drug-laboratory interactions

Interactions with laboratory tests have not been established.

SYMPTOMS AND TREATMENT OF OVERDOSE

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

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

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

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Annual Congress Registration and Hotel Details

Full Registration

- Includes all sessions of the 2010 Annual Congress from Tuesday, June 8, 2010 through Friday, June 11, 2010 and the Exhibitors' Reception on Wednesday June 9, 2010.

One-Day Registration

- Includes all sessions for the day registered. Note: Wednesday One-Day Registrants can attend the Exhibitors' Reception on June 9, 2010.

How to Register

- You can register online at www.cnsfederation.org.
- Registration forms are also available in the middle of the Preliminary Program which you will receive in mid-February. You can scan/email, mail or fax to:

  Advance Group Conference Management
  Suite 101 - 1444 Alberni Street
  Vancouver, BC, Canada V6G 2Z4
  Fax: (604) 685-3521
  Email: cnsfreg@advance-group.com

Accommodation Information

We need your help! Please support the CNSF Congress by booking your accommodations in one of the official Congress hotels, the Quebec Hilton or the Delta Quebec. The CNSF has a block of rooms reserved and has established preferential rates for conference delegates. Both hotels are conveniently located next to the convention centre and feature conference rates that are the lowest you'll find in the vicinity.

If we don't meet the minimum number of delegate reservations, the CNSF Congress will be subject to substantial financial penalties; ultimately these penalties result in a more expensive Congress registration fees in following years. Please show your support and help us by staying at one of our Official hotels! Your loyalty and commitment is appreciated.

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• Reservations process: Advance Group accepts hotel requests online at www.cnsfederation.org , in writing via fax (604) 685-3521 or by mail using the CNSF Hotel Reservation Form included in the Preliminary Program. Reservations will not be accepted by telephone.

This Just In!!!

CNSF 2010 Congress delegates who register and stay at the Quebec City Hilton for a minimum of three consecutive nights during the CNSF Congress June 8th to 11th are eligible for a draw for: a free two nights stay with one buffet breakfast for 2 people and one dinner for 2 people at the Hilton's Allegro restaurant (table d'hôte menus, no alcohol). This prize must be taken between July 1st 2010 and March 31st, 2011. This prize is not redeemable for cash.

2010 Congress Breaking News!

Dr. James Orbinski has accepted our invitation to speak as the Distinguished Guest Lecturer at the 2010 Congress of the Canadian Neurological Sciences Federation (June 8 - 11).

Dr. Orbinski is a veteran of many of the world's most disturbing and complex humanitarian emergencies. He accepted the Nobel Peace Prize on behalf of Medecins Sans Frontieres (Doctors Without Borders) in 1999.

A brilliant and mesmerizing orator, Orbinski offers a compelling look at the ravages of genocide and civil war, the role of humanitarianism, and the conflict that arises from combining humanitarian assistance with a political agenda.

Orbinski is an outspoken and passionate speaker who is deeply committed to the core principles of volunteerism and impartiality, with a belief that everyone deserves both medical assistance and the recognition of his or her humanity.assistance and the recognition of his or her humanity.

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Bring your camera!!!

Québec City is truly one of the most beautiful cities in Canada. Visitors can explore the historic downtown core as it was an original walled city with the Chateaux Frontenac overlooking the St. Lawrence seaway.

Rich in French culture and history, Québec City is known for its antique shops where treasures can be found around every corner. As the capital of Québec, Québec City is a "must see" for any traveler to Canada.

Welcome to Quebec!!

Join us for the Canadian Neurological Sciences Federation's 45th Annual Congress June 8-11, 2010

Apportez votre appareil-photo!!!

Québec est réellement l'une des plus belles villes du Canada. Les visiteurs peuvent arpenter le centre historique, car il s'agissait à l'origine d'une ville fortifiée avec le Château Frontenac surplombant la voie maritime du Saint-Laurent.

Riche d'une culture et d'un passé français, Québec est réputée pour ses magasins d'antiquités où des trésors abondent à chaque carrefour. En tant que capitale du Québec, la ville de Québec est incontournable pour tous les voyageurs qui viennent au Canada.

Bienvenue à Québec!!

45e congrès annuel de la Fédération des Sciences neurologiques du Canada - 8-11 juin 2010 Québec, Québec

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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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