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.
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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:

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

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

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Cover Letter

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

Abstracts

Original Articles should be accompanied by a Structured abstract of 250 words or less on a separate page, in either English or French. The Journal will provide translation to the other language if required. Abstracts should consist of four paragraphs headed: Background (or objective), Methods, Results and Conclusions. Review articles should be accompanied by an Unstructured abstract of 150 words or less. Brief Communications (Case Reports) require no Abstract.

Acknowledgements

Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text. The SI system (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.

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.

INFORMATION FOR AUTHORS SUBMISSION PROCESS *(continued)*

Brief Communications

Brief Communications (formerly Case Reports) are published on various topics and should be limited to approximately 9 double-spaced manuscript pages (3 Journal pages), including references (limit to approx. 5 references) and may include illustrations and tables. Brief Communications do not require an abstract.

Editor Correspondence

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

Critically Appraised Topics (CATs)

Current research in clinical neurosciences. Each CAT will appraise one or two recent research articles dealing with a particular topic. Meta-analyses and systematic reviews will also be considered if pertaining to evidence-based neurological/neurosurgical practice. A complete CAT is a one or 2 page summary that includes all of the following:

A brief title that summarizes the conclusion reached about the article.

Clinical Bottom Lines consisting of short statements summarizing the key "take-home" points. The clinical problem which cues the reader to the nature of the case. The clinical problem comes from real life dilemmas that are faced by clinicians. The clinical question includes the patient, intervention, comparator, and outcome.

The search strategy - including search terms, search engines used, and the reasons why the article chosen is the best evidence for the clinical question.

The evidence is described briefly including the type of study, patient population, and outcomes reported for the article reviewed.

The data is usually presented in tabular form and highlights the clinically significant data such as number needed to treat, specificity, hazard ratios, etc.

Comments are added regarding the quality of the study and any concerns which were identified by the critical appraisal process.

The reference, the appraiser, the date appraised, and the date expired.

Lastly, it will include a clinical comment from an "expert" on the particular topic.

Neuroimaging Highlights

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

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

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

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

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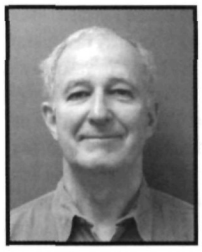

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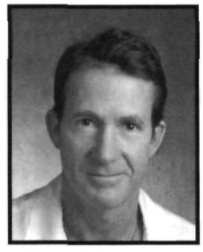

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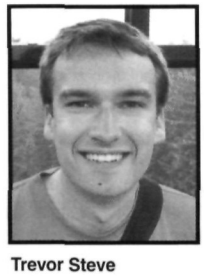

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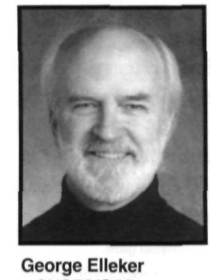

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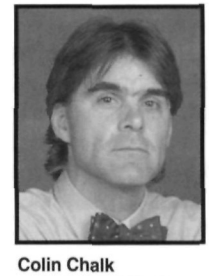

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CNSS - *Canadian Neurosurgical Society;* CSCN - *Canadian Society of Clinical Neurophysiologists;* CACN - *Canadian Association of Child Neurology;*
CBANHC - *Canadian Brain and Nerve Health Coalition*

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

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Migraine Therapy

INDICATIONS AND CLINICAL USE

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

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

CONTRAINDICATIONS

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

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

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

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

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

SPECIAL POPULATIONS

Pregnant women

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

Nursing women

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

Pediatrics (<18 years of age)

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

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

Geriatrics (>65 years of age)

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

Safety Information

WARNINGS AND PRECAUTIONS

General

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

CYP3A4 inhibitors

See CONTRAINDICATIONS above.

Cardiovascular

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hepatic

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

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

Neurologic

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

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

Psychomotor effect

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

Renal

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

Sensitivity/resistance

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

ADVERSE REACTIONS

Adverse drug reaction overview

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

Typical 5-HT_1 agonist adverse reactions

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

Increases in blood pressure

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

Clinical trial adverse drug reactions

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

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

DRUG INTERACTIONS

Effects of other drugs on eletriptan

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

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

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

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

Drug-food interactions

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

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

Administration

Dosing considerations

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

Recommended dose and dosage adjustment

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

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

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

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

The maximum daily dose should not exceed 40 mg.

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

Patients receiving potent CYP3A4 inhibitors

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

Patients with hepatic impairment

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

Patients with renal impairment

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

Administration

RELPAX tablets should be swallowed whole with water.

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Study References

1. RELPAX Product Monograph, Pfizer Canada Inc., March 2006.
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3. Mathew NT *et al.* Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache* 2003;43:214-222.
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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, these 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, hemalemesis, 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: hyperkinesia, 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_{50} of about 41 µM), this effect should not interfere with metabolism of other drugs when eletriptan is used at recommended doses. There is no *in vitro* or *in vivo* evidence that clinical doses of eletriptan will induce drug metabolizing enzymes. Therefore, eletriptan is unlikely to cause clinically important drug interactions mediated by these enzymes.

Drug-herb interactions

Interactions with herbal products have not been established.

Drug-laboratory interactions

Interactions with laboratory tests have not been established.

SYMPTOMS AND TREATMENT OF OVERDOSE

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

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

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

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