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

Acknowledgements

Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text. The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

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

Titles of journals should be abbreviated according to the style used in Index Medicus. References should list the names of up to six authors; if there are more, cite the first SIX, then et al.

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Examples of correct forms of reference:

Journals

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

Chapter in a book

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

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

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

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

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COPAXONE®
(glatiramer acetate injection)

Treating RRMS for the long run.

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Immunomodulator

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

Safety Information

WARNINGS

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

ADMINISTRATION

DOSAGE AND ADMINISTRATION

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

SUPPLEMENTAL PRODUCT INFORMATION

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

See our AD on pages A-5

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CALENDAR OF EVENTS

November 5-7, 2008
Ottawa, Ontario, Canada
DIA's 6th Canadian Annual Meeting: Benefits and Risk Management: An Evolution in Progress
To register contact: Joanne Wallace (215) 442-6180, email joanne.wallace@diahome.org or visit our website www.diahome.org

November 6-7, 2008
Phoenix, Arizona, USA
Adding, Updating, and Expanding Stroke Programs and Service Lines
For more information, please go to our website www.acius.net

November 9-11, 2008
Houston, Texas, USA
Goodman Oral Board Preparation: Neurosurgery Review by Case Management
For more information or to register, please visit www.AANS.org or email epm@aans.org

November 13-15, 2008
Sicily, Italy
European Charcot Foundation Symposium 2008. Multiple Sclerosis and Gender
Programme and more information available via www.charcot-ms.eu.

November 16-18, 2008
Valencia, Spain
International symposium on rare diseases - Inherited Neuromuscular Diseases: Translation from Pathomechanisms to Therapies
To register go to www.fundacioncac.es/catedrasg

December 5-9, 2008
Seattle, Washington, USA
2nd North American Epilepsy Congress
For more information contact info@aesnet.org or go to our website at www.aesnet.org

February 16-17, 2009
Tel Aviv, Israel
5th Annual Update Symposium on Clinical Neurology and Neurophysiology
For more information, please visit our website at: www.neurophysiology-symposium.com

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

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

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

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

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

May 7-9, 2009
Vancouver, British Columbia, Canada
International Vocational Outcomes in Traumatic Brain Injury Conference 2009
For information go to: www.tbicvancouver.com

June 9-12, 2009
Halifax, Nova Scotia, Canada
44th Annual Congress of the Canadian Neurological Sciences Federation
For more information go to: www.cnsfederation.org or contact the secretariat office at (403) 229-9544.

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

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

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

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Once-a-day Aricept®

donepezil HCl 5 & 10 mg tablets

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Cholinesterase inhibitor

INDICATIONS AND CLINICAL USE

ARICEPT (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type.

Efficacy of **ARICEPT** in patients with mild-to-moderate Alzheimer's disease (AD) was established in two 24-week and one 54-week placebo-controlled trials. Efficacy in patients with severe AD was established in two 24-week/6-month placebo-controlled trials.

ARICEPT tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of AD.

CONTRAINDICATIONS

ARICEPT (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

SPECIAL POPULATIONS

Use in pregnant or nursing women

The safety of **ARICEPT** during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant.

Use in children

There are no adequate and well-controlled trials to document the safety and efficacy of **ARICEPT** in any illness occurring in children. Therefore, **ARICEPT** is not recommended for use in children.

Use in elderly patients (≥65 years of age)

In AD patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age, and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as AD can be associated with significant weight loss, caution is advised regarding the use of **ARICEPT** in low body weight elderly patients, especially in those ≥85 years old.

Use in elderly patients with comorbid disease

There is limited safety information for **ARICEPT** in patients with mild-to-moderate or severe AD and significant comorbidity. The use of **ARICEPT** in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for adverse events (AEs). Caution is advised regarding the use of **ARICEPT** doses above 5 mg in this patient population.

In severe AD, the possibility of comorbid vascular disease and risk factors for vascular AEs and mortality should be considered.

Use in patients with vascular dementia

Three clinical trials, each of 6 months duration, were conducted to evaluate the safety and efficacy of **ARICEPT** for the symptomatic treatment of individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients with dementia that appears to be due solely to vascular causes, and to exclude patients with AD. **ARICEPT** was not shown to be an effective treatment for patients with VaD in 2 of these clinical trials.

The safety profile from these controlled clinical trials in VaD patients indicates that the rate of occurrence of treatment-emergent AEs overall was higher in VaD patients (86%) than in AD patients (75%). This was seen in both **ARICEPT**-treated subjects and placebo-treated subjects, and may relate to the greater number of comorbid medical conditions in the VaD population. In 2 of the clinical trials, there was a higher rate of mortality among patients treated with **ARICEPT**, during double-blind treatment; this result was statistically significant for 1 of these 2 trials. For the 3 VaD studies combined, the mortality rate in the **ARICEPT** group (1.7%, 25/1,475) was numerically higher than in the placebo group (1.1%, 8/718), but this difference was not statistically significant (see **Supplemental Product Information** below).

There is no evidence of an increased risk of mortality when **ARICEPT** is used in patients with mild-to-moderate AD.

Safety Information

WARNINGS AND PRECAUTIONS

Cardiovascular

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials in AD, most patients with serious cardiovascular conditions were excluded. Patients, such as those with controlled hypertension (DBP<95 mmHg), right bundle branch blockage, and pacemakers, were included. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes have been reported in association with the use of **ARICEPT**. It is recommended that **ARICEPT** should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

Gastrointestinal

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs) including high doses of acetylsalicylic acid (ASA), should be monitored for symptoms of active or occult gastrointestinal bleeding. Clinical studies of **ARICEPT** have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS** section).

ARICEPT, as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with AD, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks and have resolved during continued use of **ARICEPT** (see **ADVERSE REACTIONS** section). Treatment with the 5 mg/day dose for 4-6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance.

Genitourinary

Although not observed in clinical trials of **ARICEPT**, cholinomimetics may cause bladder outflow obstruction.

Hepatic

There is limited information regarding the pharmacokinetics of **ARICEPT** in hepatically-impaired AD patients.

Close monitoring for AEs in patients with hepatic disease being treated with **ARICEPT** is therefore recommended.

Neurologic

Seizures: Some cases of seizures have been reported with the use of **ARICEPT** in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of AD. The risk/benefit of **ARICEPT** treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

ARICEPT has not been studied in patients with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patients are unknown.

Peri-operative considerations

Anesthesia: ARICEPT, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Renal

There is limited information regarding the pharmacokinetics of **ARICEPT** in renally-impaired AD patients.

Close monitoring for AEs in patients with renal disease being treated with **ARICEPT** is therefore recommended.

Respiratory

Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **ARICEPT** has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE

Mild-to-moderate Alzheimer's disease

A total of 747 patients with mild-to-moderate AD were treated in controlled clinical studies with **ARICEPT** (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 132 days (range 1-356 days). The rates of discontinuation from controlled clinical trials of **ARICEPT** due to AEs for the **ARICEPT** 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day **ARICEPT** was higher at 13% (see Table 1). The most common AEs, defined as those occurring at a frequency of at least 5% in patients

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receiving 10 mg/day and twice the placebo rate, are largely predicted by **ARICEPT**'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia.

These AEs were often of mild intensity and transient, resolving during continued **ARICEPT** treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common AEs may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day (see Table 2 and **Supplemental Product Information** below).

Severe Alzheimer's disease

A total of 573 patients with severe AD were treated in controlled clinical studies with **ARICEPT**. Of these patients, 441 (77%) completed the studies. The duration of double-blind treatment in all studies was 24 weeks. The mean duration of treatment for all **ARICEPT** groups was 148.4 days (range 1-231 days). The mean daily dose of **ARICEPT** was 7.5 mg/day.

In clinical trials of patients with severe AD, most patients with significant comorbid conditions were excluded. The use of **ARICEPT** in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and should include close monitoring for AEs.

In controlled clinical trials in severe AD, the rate of discontinuation due to AEs was 11.3% in patients treated with **ARICEPT**, compared to 6.7% in the placebo group. The most common AEs that led to discontinuation, more often in patients treated with **ARICEPT** than placebo, were diarrhea, nausea, vomiting, urinary tract infection, decreased appetite, and aggression. Each of these AEs led to discontinuation of less than 2% of patients treated with **ARICEPT**.

The incidence profile for AEs for severe AD was similar to that of mild-to-moderate AD (see Table 4).

The most common AEs, defined as those occurring at a frequency of at least 5% in patients and twice the placebo rate, were vomiting, diarrhea, nausea, and aggression. Overall, the majority of AEs were judged by the investigators to be mild or moderate in intensity.

Results from the controlled clinical trials indicate that the incidence of AEs, such as vomiting, urinary tract infection, urinary incontinence, pneumonia, falls, decreased appetite, aggression, restlessness, hallucination and confusion, may be higher in **ARICEPT**- and placebo-treated patients with severe AD than in patients with mild-to-moderate AD.

Postmarket adverse drug reactions

Voluntary reports of AEs temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and for which there is inadequate data to determine the causal relationship with the drug, include the following: abdominal pain, cholecystitis, convulsions, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash.

DRUG INTERACTIONS

Concomitant use with other drugs

Use with anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with cholinomimetics and other cholinesterase inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists, such as bethanechol.

Use with other psychoactive drugs: Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants. There is thus limited information concerning the interaction of **ARICEPT** with these drugs.

Drug-drug interactions

Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects, evaluated the potential of **ARICEPT** for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done (see **Supplemental Product Information** below).

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

Administration

Dosing considerations

ARICEPT (donepezil hydrochloride) or **ARICEPT RDT** should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of AD.

Special populations: The use of **ARICEPT** in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for AEs. It is recommended that **ARICEPT** be used with caution in these patient populations. AEs are more common in individuals of low body weight, in patients ≥85 years old and in females.

Recommended dose and dosage adjustment

Adults: The recommended initial dose of **ARICEPT** or **ARICEPT RDT** is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** section) and to allow plasma levels to reach steady state.

Based on clinical judgement, the 10 mg daily dose may be considered following 4-6 weeks of treatment at 5 mg/day. The maximum recommended dose is 10 mg taken once daily.

Following initiation of therapy or any dosage increase, patients should be closely monitored for AEs.

Special populations: AEs are more common in individuals of low body weight, in patients ≥85 years old and in females. In elderly women of low body weight, the dose should not exceed 5 mg/day.

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

Administration

ARICEPT should be taken once daily in the morning or evening. It may be taken with or without food.

ARICEPT tablets should be swallowed whole with water.

ARICEPT RDT should be placed on the tongue and allowed to disintegrate before swallowing with water.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Use in pregnant and nursing women

Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of **ARICEPT**.

Use in elderly patients (≥65 years of age)

In controlled clinical studies with 5 and 10 mg **ARICEPT** in patients with mild-to-moderate AD, there were 536 patients between the ages of 65 to 84, and 37 patients aged ≥85 years treated with **ARICEPT**. In controlled clinical trials of patients with severe AD, there were 158 patients who were ≤74 years of age, 276 patients between the ages of 75 and 84, and 139 patients aged ≥85 years treated with **ARICEPT**.

Use in patients with vascular dementia

Mortality rates in ARICEPT vascular dementia clinical trials

Study	Placebo	ARICEPT 5 mg	*p*-value[x]	ARICEPT 10 mg	*p*-value[x]
307	3.5% (7/199)	1.0% (2/198)	0.17	2.4% (5/206)	0.57
308	0.5% (1/193)	1.9% (4/208)	0.37	1.4% (3/215)	0.62
319	0% (0/326)	1.7% (11/648)	0.02	*	NA
Combined	1.1% (8/718)	1.7% (25/1,475)			0.35

* No 10 mg **ARICEPT** treatment arm in Study 319.

[x] *p*-values are for 5 mg donepezil vs. placebo and 10 mg donepezil vs. placebo.

The majority of deaths in patients taking either **ARICEPT** or placebo appear to have resulted from various vascular-related causes, which may be expected in this elderly, fragile, population with comorbid vascular disease. In the 3 combined VaD clinical trials, there were similar proportions of patients with serious AEs in both treatment groups (approximately 15%), and similar proportions of patients with serious cardiovascular or cerebrovascular AEs (non-fatal and fatal, approximately 8%). The proportion of patients who had a fatal cardiovascular or cerebrovascular AE was numerically higher in the **ARICEPT** group than in the placebo group, but this difference was not statistically significant across the 3 trials.

ADVERSE REACTIONS

Mild-to-moderate Alzheimer's disease

The most common AEs leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most frequent adverse events in patients with mild-to-moderate Alzheimer's disease leading to withdrawal from controlled clinical trials by dose group

Dose group	Placebo	5 mg/day ARICEPT	10 mg/day ARICEPT
Number of patients randomized	355	350	315
Events/% discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common AEs were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a 1-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day.

See Table 2 for a comparison of the most common AEs following 1- and 6-week initial treatment periods with 5 mg/day **ARICEPT**.

Table 2. Comparison of rates of adverse events in patients with mild-to-moderate Alzheimer's disease treated with 10 mg/day after 1 and 6 weeks of initial treatment with 5 mg/day

	No initial treatment		1-week initial treatment with 5 mg/day	6-week initial treatment with 5 mg/day
Adverse event	**Placebo (n=315)**	**5 mg/day (n=311)**	**10 mg/day (n=315)**	**10 mg/day (n=269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

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 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT**, and for which the rate of occurrence was greater for **ARICEPT** than placebo-assigned patients. In general, AEs occurred more frequently in female patients and with advancing age.

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Table 3. Mild-to-moderate Alzheimer's disease: Adverse events reported in controlled clinical trials in at least 2% of patients receiving ARICEPT and at a higher frequency than placebo-treated patients

Body system/Adverse events	Placebo n=355	ARICEPT n=747
Percent of patients with any adverse event	**72**	**74**
Body as a whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular system		
Syncope	1	2
Digestive system		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and lymphatic system		
Ecchymosis	3	4
Metabolic and nutritional		
Weight decrease	1	3
Musculoskeletal system		
Muscle cramps	2	6
Arthritis	1	2
Nervous system		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal dreams	0	3
Somnolence	<1	2
Urogenital		
Frequent urination	1	2

Other adverse events observed during clinical trials in mild-to-moderate Alzheimer's disease

During the premarketing phase, **ARICEPT** has been administered to over 1,700 individuals with mild-to-moderate AD for various lengths of time during clinical trials worldwide. Approximately 1,200 patients have been treated for at least 3 months, and more than 1,000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1,214 days.

Treatment-emergent signs and symptoms that occurred during 3 placebo-controlled clinical trials and 2 open-label trials of patients with mild-to-moderate AD were recorded as AEs by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials experiencing that event while receiving **ARICEPT**. All AEs occurring at least twice are included. AEs already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are COSTART terms too general to be informative, or events less likely to be drug-caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/100 patients: frequent) or in <1% of patients (i.e., in 1/100 to 1/1,000 patients: infrequent). These AEs are not necessarily related to **ARICEPT** treatment, and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a whole: (≥1% and <2%) influenza, chest pain, toothache; (<1%) fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, listlessness.

Cardiovascular system: (≥1% and <2%) hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; (<1%) angina pectoris, postural hypotension, myocardial infarction, premature ventricular contraction, arrhythmia, AV Block (1st degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thromboses.

Digestive system: (≥1% and <2%) fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; (<1%) eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine system: (<1%) diabetes mellitus, goiter.

Hemic & lymphatic system: (<1%) anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Nutritional disorders: (≥1% and <2%) dehydration; (<1%) gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal system: (≥1% and <2%) bone fracture; (<1%) muscle weakness, muscle fasciculation.

Nervous system: (≥1% and <2%) delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, libido increased, restlessness, abnormal crying, nervousness, aphasia; (<1%) cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing, seizures.

Respiratory system: (≥1% and <2%) dyspnea, sore throat, bronchitis; (<1%) epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and appendages: (≥1% and <2%) abrasion, pruritus, diaphoresis, urticaria; (<1%) dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special senses: (≥1% and <2%) cataract, eye irritation, blurred vision; (<1%) dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital system: (≥1% and <2%) urinary incontinence, nocturia; (< 1%) dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Long-term safety for mild-to-moderate Alzheimer's disease

Patients were exposed to **ARICEPT** in 2 open-label extension mild-to-moderate AD studies (n=885) of over 2 years. In 1 of the studies, 763 patients who previously completed 1 of 2 placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following 1 and 2 years of treatment, 76% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative weeks 48 and 108).

Severe Alzheimer's disease

Table 4 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT**, and for which the rate of occurrence was greater for **ARICEPT** than placebo-assigned patients.

Table 4. Severe Alzheimer's disease: Adverse events reported in controlled clinical trials in at least 2% of patients receiving ARICEPT and at a higher frequency than placebo-treated patients

Body system/Adverse events	Placebo n=465	ARICEPT n=573
Percent of patients with any adverse event	**74**	**81**
Gastrointestinal		
Diarrhea	4	10
Vomiting	4	8
Nausea	3	6
Fecal incontinence	1	2
General		
Pyrexia	1	2
Chest pain	0	2
Infections and infestations		
Urinary tract infection	7	8
Nasopharyngitis	6	8
Pneumonia	3	4
Injury, poisoning, procedural complications		
Fall	9	10
Contusion	2	4
Skin laceration	1	2
Investigations		
Blood creatine phosphokinase increased	1	2
Metabolism and nutrition		
Anorexia	2	4
Decreased appetite	1	3
Dehydration	1	2
Musculoskeletal and connective tissue		
Back pain	2	3
Osteoarthritis	1	2
Nervous system		
Headache	3	5
Somnolence	0	2
Psychiatric		
Aggression	2	5
Insomnia	3	4
Restlessness	2	3
Hallucination	1	2
Confusional state	1	2
Renal and urinary		
Urinary incontinence	2	3
Respiratory		
Cough	1	2
Skin		
Eczema	1	2
Vascular		
Hypertension	1	2

A frequency of 0 has been used when frequencies were <0.5%

Other AEs that occurred with an incidence of at least 2% in **ARICEPT**-treated patients, and at an equal or lower rate than in placebo-treated patients, included: abdominal pain, fatigue, gastroenteritis, excoriation, dizziness, anxiety and depression.

Long-term safety for severe Alzheimer's disease

In Study 315, which was a 24-week, randomized, placebo-controlled study in severe AD patients, at the end of double-blind treatment, 229 patients entered open-label **ARICEPT** treatment for up to an additional 12 weeks. Therefore, at the end of the open-label phase, 111 patients had received up to 36 weeks of **ARICEPT** treatment and 118 patients had received up to 12 weeks of **ARICEPT** treatment. The most commonly affected body systems, types and frequencies of AEs reported during 12 weeks of open-label **ARICEPT** treatment were similar to what was observed during 24 weeks of double-blind treatment.

Gastrointestinal AEs (diarrhea, nausea, vomiting, anorexia) were reported at a higher frequency in patients who received up to 12 weeks of **ARICEPT** treatment. Other AEs reported at higher frequencies in patients treated with **ARICEPT** for up to 12 weeks included infection, insomnia, pneumonia, fever, dizziness, hypertension, asthenia, tremor, pharyngitis, hallucinations, convulsions and cysts.

In patients treated with **ARICEPT** for up to 36 weeks, accidental injury, urinary incontinence and urinary tract infections were reported at higher frequencies.

DRUG INTERACTIONS

Drug-drug interactions

Drugs highly bound to plasma proteins: Drug displacement studies have been performed *in vitro* between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of ARICEPT on the metabolism of other drugs: *In vitro* studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50-130 µM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 5 mg/day for 7 days had no clinically significant effect on the pharmacokinetics of ketoconazole. No other clinical trials have been conducted to investigate the effect of **ARICEPT** on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine).

It is not known whether **ARICEPT** has any potential for enzyme induction.

Effect of other drugs on the metabolism of ARICEPT: Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/day **ARICEPT** together with 200 mg/day ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30%-36%. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of **ARICEPT**.

Pharmacokinetic studies demonstrated that the metabolism of **ARICEPT** is not significantly affected by concurrent administration of digoxin or cimetidine.

Drug-food interactions

Food does not have an influence on the rate and extent of donepezil hydrochloride absorption.

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: Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Treatment: The elimination half-life of **ARICEPT** (donepezil hydrochloride) at recommended doses is approximately 70 hours. Thus, in the case of overdose, it is anticipated that prolonged treatment and monitoring of adverse and toxic reactions will be necessary. As in any case of overdose, general supportive measures should be utilized.

Tertiary anticholinergics, such as atropine, may be used as an antidote for **ARICEPT** overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether **ARICEPT** and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity observed in animals included: reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation, and lower body surface temperature.

Product Monograph available on request.

See our AD on pages A-6, A-7

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Maxalt®

rizatriptan benzoate tablets

Maxalt RPD®

rizatriptan benzoate wafers

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 and WARNINGS AND PRECAUTIONS).

For more information on adverse events associated with 5-HT$_1$ agonists see WARNINGS AND PRECAUTIONS in the Supplemental Product Information section.

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. 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 in the Product Monograph, and DOSAGE AND ADMINISTRATION).

Neurologic

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.

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 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 in the Supplemental Product Information section).

Special Populations

Pregnant Women: 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 (see WARNING AND PRECAUTIONS, Special Populations in the Product

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 (see ADVERSE REACTIONS in the Supplemental Product Information section). Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that MAXALT® does not

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 and WARNINGS AND PRECAUTIONS).

For more information on adverse events associated with 5-HT$_1$ agonists see WARNINGS AND PRECAUTIONS in the

rizatriptan benzoate tablets

rizatriptan benzoate wafers

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: 5-HT$_1$ Receptor Agonist

INDICATIONS AND CLINICAL USE

Adults

MAXALT® (rizatriptan benzoate) is indicated for the 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). 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) / Geriatrics (> 65 years of age)

The safety and efficacy of MAXALT® has not been established in these age groups and its use is not recommended (see WARNINGS AND PRECAUTIONS, Special Populations in the Product Monograph).

CONTRAINDICATIONS

MAXALT® (rizatriptan benzoate) 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), and in patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease). 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);
- in patients with uncontrolled or severe hypertension (see WARNINGS AND PRECAUTIONS);
- within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide;
- in patients with hemiplegic, ophthalmoplegic or basilar migraine;
- with concurrent administration of MAO inhibitors or within 2 weeks of discontinuation of MAO inhibitor therapy (see DRUG INTERACTIONS in the Supplemental Product Information section);
- in patients with severe hepatic impairment;
- in patients with known hypersensitivity.

SPECIAL POPULATIONS

For use in special populations, see WARNINGS AND PRECAUTIONS, Special Populations.

a patient has no response to the first
the diagnosis of migraine should be
administration of a second dose.

Psychomotor Effect: Dizziness, somn
fatigue (see ADVERSE REACTIONS i
Product Information section). Patients
to avoid driving a car or operating ha
until they are reasonably certain that
adversely affect them.

Cardiovascular

**Risk of Myocardial Ischemia and/
Other Adverse Cardiac Events:**

MAXALT® has been associated wi
and/or neck pain and tightness wh
angina pectoris. Following the u
agonists, in rare cases these sym
identified as being the likely result
spasm or myocardial ischemia. Ra
coronary events or arrhythmia have
use of other 5-HT$_1$ agonists, and
occur with MAXALT®. Because of t
class of compounds (5-HT$_{1B/1D}$ a
coronary vasospasm, MAXALT® sh
to patients with documented ische
coronary artery disease (see CON
It is strongly recommended that
given to patients in whom unrec
artery disease (CAD) is predicted
risk factors (e.g., hypertension, hyp
smoker, obesity, diabetes, strong fa
female with surgical or physiologi
male over 40 years of age) unless
evaluation provides satisfactory
that the patient is reasonably free
and ischemic myocardial disease
underlying cardiovascular disease
cardiac diagnostic procedures to de
disease or predisposition to coronar
is unknown. If, during the cardiova
the patient's medical history, elect
other investigations reveal findin
consistent with, coronary artery va
cardial ischemia, MAXALT® should n
(see CONTRAINDICATIONS).

For patients with risk factors pred
are considered to have a satisfact
evaluation, the first dose of riza
administered in the setting of a
or similar medically staffed and
Because cardiac ischemia can oc
of clinical symptoms, consideration
obtaining on the first occasion of us
gram (ECG) during the interval im

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

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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 in the Product Monograph).

ADVERSE REACTIONS

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 and WARNINGS AND PRECAUTIONS).

For more details on adverse drug reactions reported during clinical trials, see ADVERSE REACTIONS in the Supplemental Product Information section.

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: Angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, urticaria, rash, toxic epidermal necrolysis.

Musculoskeletal: Facial pain.

Special Senses: Dysgeusia.

Nervous System: Serotonin syndrome.

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

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations

MAXALT® is recommended only for the acute treatment of migraine attacks and 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

The recommended single adult dose of MAXALT® Tablets and MAXALT RPD® Wafers 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 ACTIONS AND CLINICAL PHARMACOLOGY, Clinical Studies 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 in the Supplemental Product Information section).

Renal Impairment: If treatment is deemed advisable in hemodialysis patients with severe renal impairment (creatinine clearance <2 mL/min/1.73 m^2), 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: 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: In patients with mild to moderate controlled hypertension, patients should be treated cautiously at the lowest effective dose.

Missed Dose

If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

Study References

1. Data on file, Merck Frosst Canada Ltd.: MAXALT® — Product Monograph, 2007.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Cardiovascular

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.

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.

Other Vasospasm-Related Events: 5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market 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.

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.

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.

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

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: In controlled clinical trials the most common adverse events during treatment with MAXALT® Tablets 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.

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.

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.

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.

Other Events Observed in Association with the Administration of MAXALT®: The frequencies of less commonly reported adverse clinical events are presented in the ADVERSE REACTIONS section of the Product Monograph. 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. The adverse experience profile seen with MAXALT RPD® Wafers was similar to that seen with MAXALT® Tablets.

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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DRUG INTERACTIONS

Drug-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-HT1 agonists within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

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

Selective Serotonin Reuptake Inhibitors / Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:
In a pharmacokinetic study with paroxetine and rizatriptan, paroxetine had no influence on the plasma levels of rizatriptan and no symptoms of serotonin syndrome emerged. Cases of life-threatening serotonin syndrome have however been reported in post-marketing experience during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see WARNINGS AND PRECAUTIONS.)

Drug-Food Interactions: 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.

Drug-Herb Interactions: Interactions with herbal products have not been studied.

Drug-Laboratory Interactions: MAXALT® is not known to interfere with commonly employed clinical laboratory tests.

Drug-Lifestyle Interactions: Lifestyle interactions have not been established.

OVERDOSAGE

No overdoses of MAXALT® were reported during clinical trials (for more details see OVERDOSAGE in the Product Monograph).

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.

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See our AD on page A-5

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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 may be useful in the management of central neuropathic pain in adult patients for which it has been issued marketing authorization with conditions to reflect the promising nature of the clinical evidence and the need for a confirmatory study to verify its clinical benefit. Patients should be advised of the nature of the authorization.

CONTRAINDICATIONS: Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Tumorigenic Potential: In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Ophthalmological Effects: In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see Product Monograph, **Post-Marketing Adverse Drug Reactions**).

Patients should be informed that if changes in vision occur, they should notify their physician.

Peripheral Edema: In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5508) compared with 2% of patients (42/2,384) in the placebo group. In these studies, 0.5% (28/5508) of pregabalin patients and 0.2% (4/2,384) of placebo patients withdrew due to peripheral edema (see Product Monograph, **ADVERSE REACTIONS, Peripheral Edema**).

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA (pregabalin) and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co administering LYRICA and these agents.

Congestive Heart Failure: In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate (between 0.1% and 1%; see Product Monograph, **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions)**.

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see Product Monograph, **ADVERSE REACTIONS, Post-marketing Adverse Drug Reactions)**. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic pain indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Weight Gain: Pregabalin treatment was associated with weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain (see Product Monograph, **ADVERSE REACTIONS, Weight Gain**). Pregabalin-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see Product Monograph, **WARNINGS AND PRECAUTIONS, Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Dizziness and Somnolence: In controlled neuropathic pain studies, pregabalin caused dizziness in 23% of patients (424/1,831) compared to 7% in placebo (58/857). Somnolence was experienced by 14% (256/1,831) and 4% (33/857) of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses.

Abrupt or Rapid Discontinuation: Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see Product Monograph, **ADVERSE REACTIONS, Adverse Events Following Abrupt or Rapid Discontinuation**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions: *Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Peripheral Neuropathic Pain*: The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema, and dry mouth. Adverse events were usually mild to moderate in intensity.

Adverse Events From a Controlled Clinical Study in Central Neuropathic Pain Associated With Spinal Cord Injury: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: somnolence, dizziness, asthenia, dry mouth, edema, myasthenia, constipation, thinking abnormal, amblyopia, and amnesia. Adverse events were usually mild to moderate in intensity.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by telephone: 1-866-234-2345.

ADMINISTRATION

Dosing Considerations

Patients with Impaired Renal Function: **Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in Supplemental Product Information).**

Adults:

Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently.

Central neuropathic pain: The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and

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tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered.

Administration: LYRICA is given orally with or without food.

Supplemental Product Information

Special Populations: ***Geriatrics (≥65 years of age):*** Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see Product Monograph, **WARNINGS AND PRECAUTIONS**, **Geriatrics >65 years of age**).

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labour and Delivery: The effects of pregabalin on labour and delivery in pregnant women are unknown.

Nursing Women: It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended (see Product Monograph, **WARNINGS AND PRECAUTIONS**, **Pediatrics**).

WARNINGS AND PRECAUTIONS: See the Product Monograph for further information on the following: tumorigenic potential, ophthalmological effects, peripheral edema, congestive heart failure, weight gain, dizziness and somnolence, sexual function/reproduction, and special populations.

DRUG INTERACTIONS

Overview: Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Drug Abuse and Dependence/Liability: Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

ADMINISTRATION

Dosage Adjustment Based on Renal Function: Dosing adjustment should be based on creatinine clearance (Cl_{cr}), as indicated in Table 1.

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table below).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (Cl_{cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a] Recommended Dose Escalation*			Dose Regimen
	Starting dose		Maximum daily dose	
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.
* Based on individual patient response and tolerability.
a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
b Supplementary dose is a single additional dose.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans: The highest known dose of pregabalin received in the clinical development program was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin.

Treatment or Management of Overdose: There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Hemodialysis: Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

AVAILABILITY OF DOSAGE FORMS

LYRICA is available in dosage strengths of 25 mg, 50 mg, 75 mg, 100 mg,* 150 mg, 200 mg,* 225 mg,* and 300 mg capsules.

* Not commercially available in Canada

For a copy of the Product Monograph or full Prescribing Information, please contact: Pfizer Canada Medical Information at 1-800-463-6001 or visit www.pfizer.ca.

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CANADIAN NEUROLOGICAL SCIENCES FEDERATION
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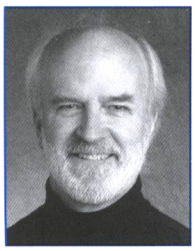

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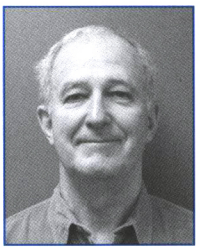

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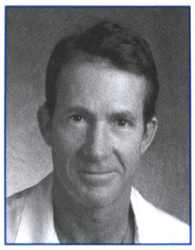

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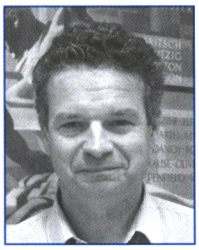

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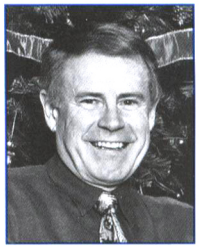

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LYRICA may be useful in the management of central neuropathic pain (NeP) in adult patients for which it has been issued marketing authorization with conditions to reflect the promising nature of the clinical evidence and the need for a confirmatory study to verify its clinical benefit. Patients should be advised of the nature of the authorization.

NEW

Pregabalin: First and only first-line analgesic with a conditional indication in central neuropathic pain

Pr LYRICA®

Powerful Pain Relief

Powerful. Fast onset. Sustained relief.

- Pain relief shown in postherpetic neuralgia (PHN) and central NeP as early as week 1 and demonstrated over 3 months[1-3*†]
- Improvement shown in pain-related sleep interference in PHN and central NeP as early as week 1 and demonstrated over 3 months[1-4*†]

Significant improvement in overall status.

- Significant improvement demonstrated in patient-reported overall status (Patient Global Impression of Change [PGIC]) ir patients with peripheral NeP [diabetic peripheral neuropathy (DPN) or PHN] and central NeP[1-3,5*†‡]

LYRICA (pregabalin) is an analgesic indicated for the management of neuropathic pain (NeP) associated with DPN and PHN.

LYRICA is contraindicated in patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

The most commonly observed adverse events (≥5% and twice the rate as that seen with placebo) were dose related for PHN and DPN patients in the recommended dose range of 150 mg/day to 600 mg/day: dizziness (9.0-37.0%), somnolence (6.1-24.7%), peripheral edema (6.1-16.2%), and dry mouth (1.9-14.9%). The most commonly observed adverse events seen in central NeP patients (≥5% and twice the rate as that seen with placebo) in the recommended dose range of 150 mg/day to 600 mg/day were: somnolence (41.4%), dizziness (24.3%), asthenia (15.7%), dry mouth (15.7%), edema (12.9%), constipation (12.9%), amnesia (10.0%), myasthenia (8.6%), amblyopia (8.6%), and thinking abnormal (8.6%). The most commonly observed adverse events in the PHN, DPN, and central NeP patients were usually mild to moderate in intensity. Discontinuation rates due to adverse events for LYRICA and placebo, respectively, were 9% and 4% in DPN, 14% and 7% in PHN and 21% and 13% in central NeP.

Dosage reduction is required in patients with renal impairment (creatinine clearance <60 mL/min) as LYRICA is primarily eliminated by renal excretion.

Please see Prescribing Information for complete Warnings and Precautions, Adverse Reactions, Dosage and Administration and patient selection criteria.

* A 13-week, multicentre, double-blind, placebo-controlled trial in 368 patients with PHN. A significant difference in pain reduction was shown over placebo for all doses: 150 mg/day, 300 mg/day, and 600 mg/day ($p \leq 0.01$, weeks 1-13). Sleep interference was improved at all time points (weeks 1 to 13 and endpoint) for the three doses evaluated ($p \leq 0.01$ vs. placebo). PGIC was reported as (at least minimally) improved by 51.2%, 47.9% and 67.1% of patients treated with LYRICA doses of 150, 300, and 600 mg/day vs. 35.5% of patients in the placebo group. At study termination, patients in the 150 mg/day ($p=0.02$) and 600 mg/day group ($p=0.003$) were more likely to report global improvement than those in the placebo group.

† Data based on a 12-week, parallel-group, double-blind, flexible-dose, placebo-controlled study. 137 patients with spinal cord injury for ≥1 year and who had a pain score ≥40 mm on the 100-mm visual analog scale (VAS) of the Short-Form-McGill Pain Questionnaire (SF-MPQ) were randomized to LYRICA 150 to 600 mg/day (n=70) or placebo (n=67) BID. Pain scores rated on 11-point numerical scale from 0 (no pain) to 10 (worst possible pain) during the past 24 hours averaged over the last seven days. Pain-related sleep interference scores rated on 11-point numerical scale from 0 (did not interfere) to 10 (completely interferes) during the past 24 hours averaged over the last seven days. A significant difference in pain reduction was demonstrated for the LYRICA group vs. placebo at all time points evaluated ($p \leq 0.001$, weeks 1-7 and endpoint and $p \leq 0.01$, weeks 8-12). Sleep interference was significantly improved at all time points (weeks 1 to 12 and endpoint) vs. placebo ($p \leq 0.01$, weeks 4, 10 and 12 and $p \leq 0.001$ for all other time points evaluated and endpoint). PGIC was reported as (at least minimally) improved by 56.5% and 21.5% of patients in the LYRICA and placebo treatment groups, respectively ($p<0.001$ for overall LYRICA comparison vs. placebo across "improved", "uncharged" and "worse" subgroups).

‡ A 12-week, multicentre, randomized, double-blind, placebo-controlled study in 338 patients with neuropathic pain [DPN (n=249) or PHN (n=89)], resulting in a significant difference from placebo in the flexible dose range 150-600 mg/day ($p \leq 0.05$, week 2-3 and $p \leq 0.01$, weeks 4-12), and the fixed dose of 600 mg/day ($p \leq 0.05$, week 1 and $p \leq 0.01$, weeks 2-12). PGIC was reported as very much improved or much improved by 52.0% of the flexible-dose group, 53.6% of the fixed-dose group and 39.5% of the placebo group ($p<0.01$ for overall comparison of both LYRICA treatment groups vs. placebo across "improved", "uncharged" and "worse" subgroups).

References: 1. Data on file, Pfizer Canada Inc., Study 1008-196. **2.** van Seventer R, Feister HA, Young JP *et al.* Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin* 2006; 22(2):375-84. **3.** Siddall PJ *et al.* Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006; 67:1792-800. **4.** LYRICA Product Monograph, Pfizer Canada Inc., November 8, 2007. **5.** Freynhagen R, Strojek K, Griesing T *et al.* Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005; 115:254-63.

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