INFORMATION FOR AUTHORS / SUBMISSION PROCESS

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As of December 1, 2007, the Canadian Journal of Neurological Sciences went to an Electronic Submission process. ALL manuscript submissions will be handled by an On-Line tracking system. Go to www.cjns.org and click on SUBMIT YOUR MANUSCRIPT and follow the instructions.

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- Figures/Images in TIF, EPS, PDF, or JPG formats
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Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication International Committee of Medical Journal Editors

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

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

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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.

Tables

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

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Neuroimaging Highlights

Neuroimaging highlights are selected by the editor-in-chief and neuroimaging highlight editors on the basis of two factors. The first is high quality "state of the art" imaging of a novel and uncommon (or common with an uncommon twist) neurological or neurosurgical disorder. The second factor is the clinical novelty of the case.

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

Images should be of the highest quality, submitted 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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Starting

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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.

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*).

Adjustment of Dose in Renally-Impaired Patients: In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table 4 in **Supplemental Product Information**).

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*).

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.

In clinical studies across various patient populations, comprising 6,396 patient-years of exposure in 8,666 patients ranging in age from 12 to 100 years, new or worsening-preexisting tumors were reported in 57 patients. The most common malignant tumor diagnosed was skin carcinoma (17 patients) followed by breast carcinoma (8 patients), prostatic carcinoma (6 patients), carcinoma not otherwise specified (6 patients), and bladder carcinoma (4 patients). Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA (pregabalin), it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

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*).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3,600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin treated and 2% of placebo-treated patients. At this time, clinical significance of the ophthalmologic findings is unknown.

Patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment, including discontinuation of pregabalin, should be considered. More frequent assessments should be considered for patients who are already routinely monitored for ocular conditions.

Peripheral Edema: In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5,508) compared with 2% of patients (42/2,384) in the placebo group. In these studies, 0.5% (28/5,508) 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. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

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.

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Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

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. In these studies, dizziness and somnolence led to withdrawal of 3.5% and 2.6% of the pregabalin-treated patients, respectively. For the remaining patients (359 and 208, respectively) who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 43% and 58% of the patients, respectively (see Product Monograph, **ADVERSE REACTIONS**, *Tables 2 and 4, and* **Post Marketing Adverse Drug Reactions**).

Accordingly, patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental and/or motor performance adversely.

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 (see Supplemental Product Information)

Clinical Trial Adverse Drug Reactions: In all controlled and uncontrolled trials during the pre-marketing development of pregabalin, more than 8,666 patients have received LYRICA (pregabalin), with 83% of exposure at dosages of 300 mg/day or above and 32% at dosages of 600 mg/day or higher. Approximately 4,010 patients had at least 6 months of exposure, 2,415 had at least 1 year of exposure, and 939 had at least 2 years of exposure to pregabalin. In controlled trials, 1,831 patients with neuropathic pain received pregabalin.

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.

In a controlled study of central neuropathic pain due to spinal cord injury, 137 patients were randomized to receive placebo (N=67) or escalating doses (150-600 mg/day) of pregabalin (N=70). The controlled study was followed by an open-label trial in which 103 patients received pregabalin (150-600 mg/day). The median duration of therapy across the double-blind and open-label studies for those subjects treated in the open-label extension was 608 days (range 14-1,248). Sixty-nine (67%) subjects received at least 1 year of open-label pregabalin and 31 (30.1%) received at least 2 years of open-label pregabalin.

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.

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.

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).**

In accordance with current clinical practice, if LYRICA (pregabalin) has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week (see Product Monograph, **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**).

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 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

Sexual Function/Reproduction

Impairment of Male Fertility, Human Data: Due to the small sample size and short-term exposure to pregabalin (only one complete sperm cycle), no conclusions can be made regarding possible reproductive effects of pregabalin during long-term exposure. Effects on other male reproductive parameters in humans have not been adequately studied.

Special Populations

Creatine Kinase Elevations: Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes, Decreased Platelet Count: Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x 10^3/µL, compared to 11 x 10^3/µL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/µL.

In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes, PR Interval Prolongation: Pregabalin treatment was associated with mild PR interval prolongation.

ADVERSE REACTIONS

Incidence of Adverse Events in Pre-marketing Controlled Clinical Studies of Neuropathic Pain: In summaries of adverse events, investigator's terms for individual adverse events have been grouped into a smaller number of standardized categories using the COSTART IV dictionary. The prescriber should be aware that the percentages in the following tables cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Adverse Events From Pre-marketing Controlled Clinical Studies of Neuropathic Pain

Diabetic Peripheral Neuropathy: Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of

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patients with neuropathic pain associated with diabetic peripheral neuropathy receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 979 patients received pregabalin and 459 patients received placebo for up to 13 weeks.

Table 1. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

Body System Preferred Term	Placebo (N=459) %	Pregabalin (mg/day) 75 (N=77) %	150 (N=212) %	300 (N=321) %	600 (N=369) %
Body as a whole					
Infection	6.1	3.9	7.5	8.4	4.6
Asthenia	2.4	3.9	1.9	4.4	7.3
Pain	3.9	5.2	4.2	2.5	4.9
Accidental injury	2.8	5.2	2.4	2.2	5.7
Back pain	0.4	0.0	2.4	1.2	1.9
Chest pain	1.1	3.9	1.4	1.2	1.6
Face edema	0.4	0.0	0.9	0.9	2.2
Digestive system					
Dry mouth	1.1	2.6	1.9	4.7	6.5
Constipation	1.5	0.0	2.4	3.7	6.0
Diarrhea	4.8	5.2	2.8	1.9	3.0
Flatulence	1.3	2.6	0	2.2	2.7
Vomiting	1.5	1.3	0.9	2.2	1.1
Hemic and lymphatic system					
Ecchymosis	0.2	2.6	0.5	0.6	0.3
Metabolic and nutritional disorders					
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Edema	0.0	0.0	1.9	4.0	1.9
Hypoglycemia	1.1	1.3	3.3	1.6	1.1
Nervous system					
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Neuropathy	3.5	9.1	1.9	2.2	5.4
Ataxia	1.3	6.5	0.9	2.2	4.3
Vertigo	1.1	1.3	1.9	2.5	3.5
Confusion	0.7	0.0	1.4	2.2	3.3
Euphoria	0.0	0.0	0.5	3.4	1.6
Thinking abnormal[a]	0.0	1.3	0.0	0.9	3.0
Abnormal gait	0.0	1.3	0.0	0.6	2.7
Reflexes decreased	1.7	3.9	0.5	1.2	1.4
Amnesia	0.2	2.6	0.9	0.0	2.2
Hypesthesia	0.7	2.6	0.0	0.0	0.8
Hyperalgesia	0.2	2.6	0.0	0.0	0.3
Respiratory system					
Dyspnea	0.7	2.6	0.0	1.9	1.9
Skin and appendages					
Pruritus	1.3	2.6	0.0	0.9	0.0
Special senses					
Blurred vision[b]	1.5	2.6	1.4	2.8	5.7
Conjunctivitis	0.2	2.6	1.4	0.6	0.3

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Postherpetic Neuralgia: Table 2 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with postherpetic neuralgia receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 852 patients received pregabalin and 398 patients received placebo for up to 13 weeks.

Table 2. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

Body System Preferred Term	Placebo (N=398) %	Pregabalin (mg/day) 75 (N=84) %	150 (N=302) %	300 (N=312) %	600 (N=154) %
Body as a whole					
Infection	3.5	14.3	8.3	6.4	2.6
Headache	5.3	4.8	8.9	4.5	8.4
Pain	3.8	4.8	4.3	5.4	4.5
Asthenia	4.0	3.6	5.0	2.6	5.2
Accidental injury	1.5	3.6	2.6	3.2	5.2
Flu syndrome	1.3	1.2	1.7	2.2	1.3
Face edema	0.8	0.0	1.7	1.3	3.2
Malaise	1.0	2.4	0.3	0.6	0.0
Cardiovascular system					
Vasodilatation	1.3	2.4	1.0	0.6	0.0
Digestive system					
Dry mouth	2.8	7.1	7.0	6.1	14.9
Constipation	2.3	3.6	4.6	5.4	5.2
Diarrhea	4.0	2.4	4.3	3.5	4.5
Flatulence	1.0	2.4	1.3	1.6	3.2
Vomiting	0.8	1.2	0.7	2.9	2.6
Metabolic and nutritional disorders					
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Weight gain	0.3	1.2	1.7	5.4	6.5
Edema	1.3	0.0	1.0	2.2	5.8
Hyperglycemia	0.8	2.4	0.3	0.0	0.0
Nervous system					
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Ataxia	0.5	1.2	2.0	5.4	9.1
Abnormal gait	0.5	0.0	2.0	3.8	7.8
Confusion	0.3	1.2	2.3	2.9	6.5
Thinking abnormal[a]	1.5	0.0	1.7	1.3	5.8
Incoordination	0.0	2.4	1.7	1.3	2.6
Amnesia	0.0	0.0	1.0	1.3	3.9
Speech disorder	0.0	0.0	0.3	1.3	3.2
Insomnia	1.8	0.0	0.7	2.2	0.0
Euphoria	0.0	2.4	0.0	1.3	1.3
Nervousness	0.5	0.0	1.0	0.3	2.6
Tremor	1.5	1.2	0.0	1.0	2.6
Hallucinations	0.0	0.0	0.3	0.3	3.2
Hyperesthesia	0.3	2.4	0.3	0.0	1.3
Respiratory system					
Bronchitis	0.8	0.0	1.3	1.0	2.6
Pharyngitis	0.8	0.0	2.6	0.6	0.6
Rhinitis	1.8	1.2	0.7	0.6	3.2
Skin and appendages					
Rash	3.0	2.4	2.0	2.9	5.2
Special senses					
Blurred vision[b]	2.5	1.2	5.0	5.1	9.1
Diplopia	0.0	0.0	1.7	1.9	3.9
Abnormal vision	0.3	0.0	1.0	1.6	5.2
Urogenital system					
Urinary tract infection	1.5	0.0	2.3	1.6	3.2

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Adverse Events From a Controlled Clinical Study in Central Neuropathic Pain Associated With Spinal Cord Injury

Table 3 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving pregabalin and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients had adverse events with a maximum intensity of mild or moderate. In this study, 70 patients received pregabalin and 67 patients received placebo for up to 12 weeks.

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in a Placebo-Controlled Study in Central Neuropathic Pain Associated With Spinal Cord Injury (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

Body System Preferred Term	Placebo (N=67) %	Pregabalin (150-600 mg/day) (N=70) %
Body as a whole		
Asthenia	6.0	15.7
Infection	6.0	8.6
Abdomen enlarged	0.0	4.3
Pain	1.5	4.3
Back pain	1.5	2.9
Cellulitis	0.0	2.9
Flu syndrome	1.5	2.9
Neck pain	1.5	2.9
Cardiovascular system		
Hypotension	0.0	2.9
Digestive system		
Dry mouth	3.0	15.7
Constipation	6.0	12.9
Gastroenteritis	0.0	2.9
Increased appetite	0.0	2.9

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Body System Preferred Term	Placebo (N=67) %	Pregabalin (150-600 mg/day) (N=70) %
Metabolic and nutritional disorders		
Edema	0.0	12.9
Peripheral edema	6.0	10.0
Weight gain	0.0	4.3
Musculoskeletal system		
Myasthenia	4.5	8.6
Joint disorder	0.0	2.9
Nervous system		
Somnolence	9.0	41.4
Dizziness	9.0	24.3
Amnesia	3.0	10.0
Thinking abnormal[a]	1.5	8.6
Paresthesia	1.5	5.7
Euphoria	0.0	4.3
Speech disorder	1.5	4.3
Twitching	0.0	4.3
Withdrawal syndrome	0.0	4.3
Skin and appendages		
Skin ulcer	1.5	4.3
Alopecia	0.0	2.9
Vesiculobullous rash	0.0	2.9
Special senses		
Blurred vision[b]	3.0	8.6
Diplopia	1.5	2.9
Tinnitus	0.0	2.9
Urogenital system		
Urinary incontinence	3.0	5.7

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Adverse Events Following 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, **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**).

Drug Abuse and Dependence/Liability: In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, a single dose of LYRICA (pregabalin) 450 mg received subjective ratings of "good drug effect", "high", and "liking" to a degree that was similar to a single dose of diazepam 30 mg. In controlled clinical studies in over 5,500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event. However, in clinical trials of diabetic peripheral neuropathy, euphoria was reported as an adverse event by 1.8% of LYRICA-treated patients and 0 % of placebo-treated patients, and in clinical trials of postherpetic neuralgia, euphoria was reported as an adverse event by 0.9% of LYRICA-treated patients and 0% of placebo-treated patients. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea suggestive of physical dependence (see Product Monograph, **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**).

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: LYRICA is primarily eliminated by renal excretion. Therefore, the dose should be adjusted for patients with reduced renal function. Pregabalin clearance is directly proportional to creatinine clearance. Therefore, dosing adjustment should be based on creatinine clearance (Cl_{cr}), as indicated in Table 4.

To use this dosing table, an estimate of the patient's creatinine clearance (Cl_{cr}) in mL/min is needed. Cl_{cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$Cl_{cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

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 4. 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.

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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CALENDAR OF EVENTS

May 25-28, 2008
Montreal, Quebec, Canada
2nd Annual Canadian Neuroscience Meeting jointly organized by CAN and INMHA
For further information about the venue, programme and accomodations go to www.can-acn2008.org.

May 25-27, 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

June 6-9, 2008
Toronto, Ontario, Canada
Canadian College of Neuropsychopharmacology (CCNP) Annual Conference
For more information contact Ms. Rachelle Anderson at (780) 407-6543 (Tel) or (780) 407-6672 (Fax) or email rmena@ualberta.ca. Visit our website www.ccnp.ca.

June 15-19, 2008
Melbourne, Australia
2008 Organization for Human Brain Mapping Meeting
Please visit www.hbm2008.com for more information.

June 17-20, 2008
Victoria, British Columbia, Canada
43rd 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.

June 19, 2008
Victoria, British Columbia, Canada
5th Annual CANN Run/Walk for Nursing Research - 5KM RUN or 3-5KM WALK
For more information contact wilma.koopman@lhsc.on.ca or dhohowe@aol.com

June 25-26, 2008
Montreal, Quebec, Canada
Spinal Cord: Function, Repair and Rehabilitation after Injury
Call for Abstract and Registration is now open. For more information please go to http://www.emrl.ca/spinalcord2008.html

September 5-6, 2008
Toronto, Ontario, Canada
9th Annual Interventional Neuroradiology Symposium
For more information contact the Office of Continuing Education and Professional Development, E-mail: help-MIM0804@cmetoronto.ca or go to our website: www.cme.utoronto.ca

September 17-20, 2008
Montreal, Quebec, Canada
World Congress on Treatment and Research in Multiple Sclerosis
Please visit www.msmontreal for more information on program, registration and abstract submission.

October 5-7, 2008
Vancouver, British Columbia, Canada
7th North American Conference on Shaken Baby Syndrome (Abusive Head Trauma)
For information go to: www.dontshake.org

October 23-26, 2008
Athens, Greece
Controversies in Neurology (CONy)
For additional information regarding CONy, please visit our website: www.comtecmed.com/cony

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

January 16-18, 2009
Orlando, Florida, USA
AAN Annual Meeting
For information go to: www.aan.com/fall07

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

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.

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

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 vascular dementia in two 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 two 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 one of these two trials. For the three 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 increase 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.

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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 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.

Study References

1. Seltzer B *et al.* Efficacy of donepezil in early-stage Alzheimer disease. *Arch Neurol* 2004;61:1852-1856.
2. Rogers SL *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136-145.

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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 three 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 three 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.

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 (first 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.

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BETASERON®
INTERFERON BETA 1b
Act early. Act strong.

PRESCRIBING SUMMARY

PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION: Immunomodulator

INDICATIONS AND CLINICAL USE: BETASERON (interferon beta-1b) is indicated for:

- The treatment of patients with a single demyelinating event accompanied by at least two clinically silent lesions typical of multiple sclerosis (MS) on magnetic resonance imaging, to delay progression to definite MS. Before initiating treatment with BETASERON, alternate diagnoses should first be excluded.
- The reduction of the frequency of clinical exacerbations in ambulatory patients with relapsing-remitting multiple sclerosis. Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery.
- The slowing of progression in disability and the reduction of the frequency of clinical exacerbations in patients with secondary-progressive multiple sclerosis.

The safety and efficacy of BETASERON in primary progressive MS have not been evaluated.

Pediatrics (<18 years of age): Safety and efficacy in children under 18 years of age have not been established.

Special Populations

Women of Childbearing Age: Women of childbearing potential should take reliable contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking BETASERON, the patient should discontinue therapy. It is not known if interferons alter the efficacy of oral contraceptives.

Nursing Women: It is not known whether BETASERON is excreted in human milk. Given that many drugs are excreted in human milk, there is a potential for serious adverse reactions in nursing infants, therefore a decision should be made whether to discontinue nursing or discontinue BETASERON treatment.

CONTRAINDICATIONS

- Patients with a history of hypersensitivity to natural or recombinant interferon beta, albumin human or to any other ingredient in the formulation.
- Pregnant women.

SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Cardiovascular: Rare cases of cardiomyopathy have been reported. If this occurs, and a relationship to BETASERON (interferon beta-1b) is suspected, treatment should be discontinued.

Symptoms of flu syndrome observed with BETASERON therapy may prove stressful to patients with severe cardiac conditions. Patients with cardiac disease such as angina, congestive heart failure or arrhythmia should be monitored closely for worsening of their clinical conditions.

Endocrine and Metabolism: Rare cases of thyroid dysfunction (hyper- as well as hypothyroidism) associated with the use of BETASERON have been reported.

Hepatic/Biliary/Pancreas: Rare post-market cases of serious hepatic injury, including autoimmune hepatitis, hepatitis and hepatic failure, have been reported with interferon beta treatment for multiple sclerosis.

It is recommended that liver function testing occur at baseline, every month for the first 6 months of treatment and at 6-month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALT) levels increase 5 times above the upper limit of normal.

Interferon beta therapy should be initiated with caution in patients with a history of significant liver disease or alcohol abuse and in patients with clinical evidence of acute liver disease.

Caution must be exercised when prescribing drugs with documented hepatotoxicity to patients on interferon beta therapy for multiple sclerosis.

In rare cases, pancreatitis has been observed with BETASERON use, often associated with hypertriglyceridemia.

Hypersensitivity: Serious hypersensitivity reactions (rare but severe acute reactions such as bronchospasm, anaphylaxis and urticaria) may occur.

Immune: The administration of cytokines to patients with pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.

Neurologic: Rare cases of seizures have been reported with interferon beta therapy. BETASERON should be administered with caution to patients with a history of seizure disorders.

This product contains human albumin and hence carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeld-Jacob disease (CJD) is also considered extremely remote.

The effect of BETASERON on the ability to drive and use machinery has not been investigated.

Psychiatric: Depression and suicide have been reported to occur in patients receiving interferon alpha, a related compound. Patients treated with BETASERON should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

Sexual Function/Reproduction: *Effects of BETASERON on women with normal menstrual cycles are not known.*

ADVERSE REACTIONS (see supplemental product information)

Overview: The most frequently observed adverse reactions are a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache or myalgia) and injection site reactions. Flu-like symptoms may be reduced by administration of acetaminophen or NSAIDs. Dose titration was used at the start of treatment in the clinically isolated syndrome and secondary-progressive MS studies in order to increase the tolerability of BETASERON (see DOSAGE AND ADMINISTRATION).

Clinical Trial Adverse Drug Reactions: The following adverse events were observed in placebo-controlled clinical studies of BETASERON (interferon beta-1b), at the recommended dose of 0.25 mg (8 MIU), in patients with relapsing-remitting MS (n=124), secondary-progressive MS (n=360), and in patients with a single clinical event suggestive of MS (n=292).

1. Relapsing-remitting MS: Injection site reactions (85%) and injection site necrosis (5%) occurred after administration of BETASERON. Inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated ($p<0.05$) with the 0.25 mg (8 MIU) BETASERON-treated group, compared to placebo. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7 days per year. Three patients withdrew from the 0.25 mg (8 MIU) BETASERON-treated group for injection site pain.

The most commonly reported clinical and laboratory adverse events were: injection site reaction (85% vs. 37% for placebo), headache (84% vs. 77% for placebo), lymphocytes count <1500/mm^3 (82% vs. 67% for placebo), flu-like symptom complex (76% vs. 56% for placebo), fever (59% vs. 41% for placebo), pain (52% vs. 48% for placebo), asthenia (49% vs. 35% for placebo), and chills (46% vs. 19% for placebo).

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2. Secondary-progressive MS: The most commonly reported adverse events were: lymphopenia (<1,500 mm^3) (90.9% vs. 74.3% for placebo), asthenia (63% vs. 58% for placebo), flu syndrome (61% vs. 40% for placebo), injection site inflammation (48% vs. 4% for placebo), headache (47% vs. 41% for placebo), injection site reaction (46% vs. 10% for placebo), hypertonia (41% vs. 31% for placebo), fever (40% vs. 13% for placebo), myasthenia (39% vs. 40% for placebo), and neuropathy (38% vs. 41% for placebo).

3. Single Clinical Event Suggestive of MS: The most frequent adverse events reported during the two-year study in patients treated with 8 MIU BETASERON were lymphocyte count <1,500 mm^3 (79.1% vs. 45.5%), injection site reaction (48.3% vs. 85%), flu syndrome (44.2% vs. 18.2%), headache (26.7% vs. 17%) and asthenia (21.6% vs. 17%).

The frequency of some adverse events decreased substantially from the first year to the second year of the study. The proportion of BETASERON-treated patients experiencing flu syndrome was reduced from 42% in the first year to 13% in the second year. Also, injection site reactions occurred less frequently during the second year (30%) than during the first year (46%).

DRUG INTERACTIONS

Drug-Drug Interactions: Interactions between BETASERON and other drugs have not been evaluated. Although studies designed to examine drug interactions have not been done, it was noted that BETASERON patients (n=180) have received corticosteroid or ACTH treatment of relapses for periods of up to 28 days.

BETASERON administered in three cancer patients over a dose range of 0.025 mg (0.8 MIU) to 2.2 mg (71 MIU) led to a dose-dependent inhibition of antipyrine elimination. The effect of alternate-day administration of 0.25 mg (8 MIU) BETASERON on drug metabolism in MS patients is unknown.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when BETASERON is administered in combination with agents that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance.

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: toll-free telephone: 866 234-2345; toll-free fax 866 678-6789, or by email cadrmp@hc-sc.gc.ca. To contact Bayer HealthCare Pharmaceuticals Adverse Event Reporting to report a serious or unexpected reaction(s) to this drug, please call: toll-free telephone at 1 800 265-7382; toll-free fax at 1 866 232-0565.

ADMINISTRATION

Dosing Considerations

FOR SUBCUTANEOUS USE ONLY

BETASERON (interferon beta-1b) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of multiple sclerosis.

Recommended Dose and Dosage Adjustment: The recommended dose of BETASERON for both relapsing-remitting and secondary-progressive MS patients is 0.25 mg (8 MIU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose in relapsing-remitting MS are presented in the CLINICAL TRIALS section of the Product Monograph.

Dose titration was used at the start of treatment in the clinically isolated syndrome and secondary-progressive MS studies in order to increase the tolerability of BETASERON.

In the study in patients with a single clinical event suggestive of MS (clinically isolated syndrome), dosage was increased as shown in the table below.

Schedule for Dose Titration[1]

Treatment day	Dose	Volume
1, 3, 5	0.0625 mg (2 MIU)	0.25 mL
7, 9, 11	0.125 mg (4 MIU)	0.5 mL
13, 15, 17	0.1875 mg (6 MIU)	0.75 mL
≥ 19	0.250 mg (8 MIU)	1.0 mL

[1]Titration scheme as used in the study in patients with a single clinical event suggestive of multiple sclerosis. The titration period may be adjusted if any significant adverse reaction occurs.

In the secondary-progressive MS study, patients initiated treatment with half the dose (4 MIU s.c. every other day) for a period of 2 weeks prior to escalating to the recommended dose of 8 MIU (s.c. every other day).

Efficacy of treatment for longer than 2 years has not been substantially demonstrated in relapsing-remitting multiple sclerosis. For secondary-progressive multiple sclerosis, safety and efficacy data beyond 3 years are not available.

In patients with a single clinical event suggestive of MS, efficacy has been demonstrated over a period of two years.

Missed Dose: If an injection is missed, it should be given as soon as feasible. The next injection should be given two days later.

ADMINISTRATION

Reconstitution: To reconstitute lyophilized BETASERON for injection, use the vial adapter to inject the entire contents of the prefilled diluent syringe containing Sodium Chloride 0.54% Solution into the BETASERON vial. Gently swirl the vial of BETASERON to dissolve the drug completely; do not shake. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with diluent, each mL of solution contains 0.25 mg (8 MIU) interferon beta-1b, 13 mg Albumin Human USP and 13 mg Mannitol USP.

Vial Content	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
0.3 mg interferon beta-1b	1.2 mL	1.2 mL	0.25 mg/mL

Subcutaneous injection: Withdraw 1 mL of reconstituted solution from the vial back into the syringe, fitted with a 1/2-inch needle, and inject the solution subcutaneously. Sites for self-injection include abdomen, buttocks and thighs. All components are suitable for single use only; unused portions should be discarded. (See Part III: Consumer Information, Proper Use of this Medication Section of the Product Monograph for self-injection procedure).

Supplemental Product Information

Warnings and Precautions

Dependence/Tolerance No evidence or experience suggests that abuse or dependence occurs with BETASERON therapy; however, the risk of dependence has not been systematically evaluated.

Information to be Provided to the Patient Patients should be informed of the potential risk of liver injury with interferon beta therapy, and of the requirement for frequent laboratory testing for liver function (see **Monitoring and Laboratory Tests**). Patients should be informed of the symptoms suggesting liver dysfunction, such as jaundice, malaise, fatigue, nausea, vomiting, abdominal pain, dark urine and pruritus, and advised to consult their physician immediately if such symptoms arise.

Patients should be instructed in injection techniques to assure the safe self-administration of BETASERON (see below and **PART III: CONSUMER INFORMATION**).

Monitoring and Laboratory Tests: The following laboratory tests are recommended prior to initiating BETASERON therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. It is recommended that liver function testing occur at baseline, every month for the first 6 months of treatment and at 6-month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALT) levels increase 5 times above the upper limit of normal. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating BETASERON therapy.

ADVERSE REACTIONS

1. Relapsing-remitting MS

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 MIU) BETASERON. A patient was defined as having a flu-like symptom complex if flu-like syndrome or at least two of the following symptoms were concurrently reported: fever, chills, myalgia, malaise or sweating. Only myalgia, fever and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 60% of patients experiencing the event during the first 3 months of treatment compared to 10% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3.5 days and the median duration per patient was 7.5 days per year.

Twenty-one (28%) of the 76 females of childbearing age treated at 0.25 mg (8 MIU) BETASERON and 10 (13%) of the 76 females of childbearing age treated with placebo reported menstrual disorders. All reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

Mental disorders such as depression, anxiety, emotional lability, depersonalization, suicide attempts and confusion were observed in this study. Two patients withdrew for confusion. One suicide and four attempted suicides were also reported. It is not known whether these symptoms may be related to the underlying neurological basis of MS, to BETASERON treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be monitored closely and cessation of therapy should be considered.

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to three years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been re-classified using the standard COSTART glossary to reduce the total number of terms employed in Table 1. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

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Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality) ≥ 2% and >2% Difference (BETASERON vs. Placebo) in the Relapsing-remitting MS Study

System organ class Adverse event	Placebo n=123	BETASERON 0.25 mg (8 MIU) n=124
Infections and infestations		
Sinusitis	26%	36%
Laryngitis	2%	6%
Neoplasms, benign, malignant and unspecified		
Cyst	2%	4%
Breast neoplasm	0%	2%
Blood and lymphatic system disorders		
Lymphadenopathy	11%	14%
Endocrine disorders		
Goiter	0%	2%
Metabolism and nutrition disorders		
Glucose < 55 mg/dL	13%	15%
Weight gain	0%	4%
Weight loss	2%	4%
Psychiatric disorders		
Depression	24%	25%
Anxiety	13%	15%
Nervousness	5%	8%
Suicide attempt	0%	2%
Nervous system disorders		
Dizziness	28%	35%
Hypertonia	24%	26%
Myasthenia	10%	13%
Migraine	7%	12%
Somnolence	3%	6%
Confusion	2%	4%
Speech disorder	1%	3%
Convulsion	0%	2%
Hyperkinesia	0%	2%
Amnesia	0%	2%
Eye disorders		
Conjunctivitis	10%	12%
Abnormal vision	4%	7%
Cardiac disorders		
Palpitation*	2%	8%
Tachycardia	3%	6%
Vascular disorders		
Hypertension	2%	7%
Peripheral vascular disorder	2%	5%
Hemorrhage	1%	3%
Respiratory, thoracic and mediastinal disorders		
Dyspnea*	2%	8%
Gastrointestinal disorders		
Diarrhea	29%	35%
Abdominal pain	24%	32%
Constipation	18%	24%
Vomiting	19%	21%
Gastrointestinal disorder	3%	6%
Skin and subcutaneous tissue disorders		
Sweating*	11%	23%
Alopecia	2%	4%
Necrosis	0%	2%
Musculoskeletal and connective tissue disorders		
Myalgia*	28%	44%
Pelvic pain	3%	6%
Renal and urinary disorders		
Cystitis	4%	8%
Urinary urgency	2%	4%
Reproductive system and breast disorders		
Dysmenorrhea	11%	18%
Menstrual disorder*	8%	17%
Metrorrhagia	8%	15%
Breast pain	3%	7%
Menorrhagia	3%	6%
Fibrocystic breast	1%	3%
General disorders and administration site conditions		
Injection site reaction*	37%	85%
Headache	77%	84%
Flu-like symptom complex*	56%	76%
Fever*	41%	59%
Pain	48%	52%
Asthenia*	35%	49%
Chills*	19%	46%
Malaise*	3%	15%
Generalized edema	6%	8%
Injection site necrosis*	0%	5%
Investigations		
Lymphocytes < 1500/mm^3	67%	82%
ALT (SGPT) > 5 times baseline*	6%	19%
ANC < 1500/mm^3*	6%	18%
WBC < 3000/mm^3*	5%	16%
Total bilirubin > 2.5 times baseline	2%	6%
Urine protein > 1+	3%	5%
AST (SGOT) > 5 times baseline*	0%	4%

*Significantly associated with BETASERON treatment ($p<0.05$).

2. Secondary-progressive MS

The incidence of adverse events that occurred in at least 2% of patients treated with 8 MIU BETASERON or placebo for up to three years, or where an adverse event was reported at a frequency at least 2% higher with BETASERON than that observed for placebo-treated patients in the secondary-progressive study, is presented in Table 2. Adverse events significantly associated with BETASERON compared to placebo ($p<0.05$) are also indicated in Table 2.

Table 2: Incidence of Adverse Events (Regardless of Causality) ≥ 2% or >2% Difference (BETASERON vs. Placebo) in the Secondary-progressive MS Study

System organ class Adverse event	Placebo n=358	BETASERON 0.25 mg (8 MIU) n=360
Infections and infestations		
Rhinitis	32%	28%
Urinary tract infection	25%	22%
Pharyngitis	20%	16%
Infection	11%	13%
Bronchitis	12%	9%
Sinusitis	6%	6%
Pneumonia	5%	5%
Abscess*	2%	4%
Upper respiratory tract infection	2%	3%
Herpes simplex	2%	3%
Herpes zoster	2%	1%
Blood and lymphatic system disorders		
Leukopenia*	5%	10%
Lymphadenopathy	1%	3%
Anemia	5%	2%
Ecchymosis	2%	1%
Immune system disorders		
Allergic reaction	3%	2%
Metabolism and nutrition disorders		
Weight loss	3%	2%
Hypercholesterolemia	2%	1%
Psychiatric disorders		
Depression	31%	27%
Insomnia	8%	12%
Emotional lability	11%	8%
Anxiety	5%	6%
Nervousness	3%	4%
Nervous system disorders		
Headache	41%	47%
Hypertonia*	31%	41%
Myasthenia	40%	39%
Neuropathy	41%	38%
Paresthesia	39%	35%
Abnormal gait	34%	34%
Ataxia	23%	19%
Dizziness	14%	14%
Incoordination	13%	11%
Vertigo	12%	8%
Paralysis	10%	8%
Somnolence	8%	8%
Tremor	9%	6%
Sleep disorder	5%	6%
Hypesthesia	4%	6%
Neuralgia	7%	5%
Movement disorder	6%	5%
Migraine	3%	4%
Spastic paralysis	1%	3%
Speech disorder	5%	2%
Dysarthria	4%	2%
Convulsion	2%	2%
Hyperesthesia	2%	2%
Optic neuritis	2%	2%
Amnesia	3%	1%
Hemiplegia	2%	1%
Thinking abnormal	2%	1%
Myoclonus	2%	0%
Eye disorders		
Abnormal vision	15%	11%
Amblyopia	10%	7%
Diplopia	9%	7%
Eye pain	5%	4%
Eye disorder	2%	3%
Conjunctivitis	3%	2%
Ear and labyrinth disorders		
Otitis media	3%	2%
Deafness	3%	1%
Ear disorder	2%	1%
Tinnitus	2%	1%
Cardiac disorders		
Palpitation	3%	2%
Syncope	3%	2%
Tachycardia	1%	2%
Vascular disorders		
Vasodilatation	4%	6%
Peripheral vascular disorder	5%	5%
Hypertension*	2%	4%
Hypotension	4%	2%
Hemorrhage	2%	2%
Respiratory, thoracic and mediastinal disorders		
Cough increased	10%	5%
Dyspnea	2%	3%
Sore throat	1%	2%
Asthma	2%	1%
Thorax pain	2%	1%
Voice alteration	2%	1%
Gastrointestinal disorders		
Nausea	13%	13%
Constipation	12%	12%
Abdominal pain*	6%	11%
Diarrhea	10%	7%
Gastroenteritis	5%	6%
Vomiting	6%	4%
Dysphagia	5%	4%
Gastrointestinal disorder	5%	4%
Tooth disorder	4%	4%
Dyspepsia	4%	4%
Anorexia	2%	4%
Flatulence	1%	3%
Fecal incontinence	3%	2%
Gastritis	2%	2%
Gastrointestinal pain	0%	2%
Gingivitis	0%	2%
Dry mouth	2%	1%
Colitis	2%	0%

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Skin and subcutaneous tissue disorders		
Rash*	12%	20%
Sweating increased	6%	6%
Pruritus	6%	6%
Skin disorder	4%	4%
Eczema	4%	2%
Alopecia	2%	2%
Acne	2%	2%
Dry skin	3%	1%
Subcutaneous hematoma	3%	1%
Seborrhea	2%	1%
Musculoskeletal and connective tissue disorders		
Back pain	24%	26%
Myalgia*	9%	23%
Arthralgia	20%	20%
Pain in extremity	12%	14%
Neck pain	6%	5%
Chest pain	4%	5%
Bone fracture (not spontaneous)	5%	3%
Muscle cramps	3%	3%
Spontaneous bone fracture	3%	3%
Arthritis	1%	2%
Joint disorder	1%	2%
Renal and urinary disorders		
Urinary incontinence	15%	8%
Urinary urgency	7%	8%
Urinary tract disorder	10%	7%
Cystitis	9%	7%
Increased urinary frequency	5%	6%
Urinary retention	6%	4%
Dysuria	2%	2%
Nocturia	1%	2%
Pyelonephritis	0%	2%
Kidney pain	2%	0%
Reproductive system and breast disorders		
Metrorrhagia	6%	12%
Menstrual disorder	13%	9%
Impotence	4%	7%
Vaginitis	4%	3%
Amenorrhea	4%	3%
Menopause	4%	2%
Menorrhagia	4%	2%
Vaginal moniliasis	2%	2%
Prostatic disorder	1%	2%
Breast pain	2%	1%
General disorders and administration site conditions		
Asthenia	58%	63%
Flu syndrome*	40%	61%
Injection site inflammation*	4%	48%
Injection site reaction*	10%	46%
Fever*	13%	40%
Pain	25%	31%
Chills*	7%	23%
Injection site pain	5%	9%
Malaise	5%	8%
Peripheral edema	7%	7%
Injection site necrosis*	0%	5%
Chills and fever*	0%	3%
Injection site hemorrhage	2%	2%
Investigations		
Laboratory test abnormal	1%	3%
Liver function test abnormal	1%	3%
SGPT increased	2%	2%
Injury, poisoning and procedural complications		
Accidental injury	17%	14%

*Significantly associated with BETASERON treatment ($p<0.05$).

Seventy-four (74) patients discontinued treatment due to adverse events (23 on placebo and 51 on BETASERON). Injection site reactions were significantly associated with early termination of treatment in the BETASERON group compared to placebo ($p<0.05$). The highest frequency of adverse events leading to discontinuation involved the nervous system, of which depression (7 on placebo and 11 on BETASERON) was the most common.

3. Single Clinical Event Suggestive of MS

The incidence of all adverse events reported during the two-year study duration that occurred in ≥1% of patients treated with 8 MIU BETASERON and with a higher frequency versus the placebo group is presented in **Table 3**. The most frequent adverse events reported for BETASERON were injection site reaction (48.3%), flu syndrome (44.2%), headache (26.7%) and asthenia (21.6%).

The frequency of some adverse events decreased substantially from the first year to the second year of the study. The proportion of BETASERON-treated patients experiencing flu syndrome was reduced from 42% in the first year to 13% in the second year. Also, injection site reactions occurred less frequently during the second year (30%) than during the first year (46%).

Table 3: Incidence of Adverse Events (Regardless of Causality) ≥ 1% Occurring More Frequently in BETASERON (vs. Placebo) Patients With a Single Demyelinating Event Suggestive of MS

System organ class Adverse event (Preferred term, MedDRA version 9.0)	Placebo (n=176)	BETASERON 0.25 mg (8 MIU) (n=292)
Infections and infestations		
Infection	3.4%	5.8%
Herpes simplex	1.1%	1.4%
Tooth abscess	0.6%	1.0%
Herpes zoster	0%	1.0%
Blood and lymphatic system disorders		
Leukopenia*	5.7%	18.2%
Lymphadenopathy	0.6%	1.4%
Thrombocytopenia	0.6%	1.4%
Immune system disorders		
Hypersensitivity	1.7%	4.5%
Endocrine disorders		
Hypothyroidism	1.1%	1.4%
Metabolism and nutrition disorders		
Hypoglycemia	0%	1.0%
Psychiatric disorders		
Insomnia	4.0%	8.2%
Affect lability	2.3%	4.1%
Nervousness	1.1%	1.4%
Nervous system disorders		
Headache*	17.0%	26.7%
Optic neuritis	2.3%	2.7%
Migraine	1.7%	2.4%
Hypertonia	1.1%	2.1%
Visual field defect	0%	1.4%
Hemiplegia	0.6%	1.0%
Myoclonus	0%	1.0%
Eye disorders		
Visual disturbance*	0.6%	3.4%
Eye pain	2.8%	3.1%
Vision blurred	0%	1.7%
Conjunctivitis	1.1%	1.4%
Diplopia	0.6%	1.0%
Cardiac disorders		
Palpitations	0.6%	1.4%
Tachycardia	0%	1.4%
Vascular disorders		
Hypertension	0%	2.1%
Hypotension	0%	1.4%
Respiratory, thoracic and mediastinal disorders		
Cough	2.3%	2.4%
Epistaxis	0.6%	1.4%
Gastrointestinal disorders		
Vomiting*	1.1%	5.1%
Abdominal pain	2.8%	4.8%
Diarrhea	1.7%	4.1%
Tooth disorder	1.7%	2.4%
Gastritis	0.6%	1.7%
Aphthous stomatitis	0.6%	1.4%
Constipation	0.6%	1.0%
Glossodynia	0%	1.0%
Skin and subcutaneous tissue disorders		
Rash*	2.8%	11.0%
Hyperhidrosis	1.1%	2.1%
Pruritus	1.1%	2.1%
Urticaria	0.6%	2.1%
Skin disorder	0%	1.4%
Psoriasis	0.6%	1.0%
Eczema	0%	1.0%
Musculoskeletal and connective tissue disorders		
Back pain	6.8%	9.9%
Pain in extremity	3.4%	6.2%
Arthralgia	5.7%	5.8%
Renal and urinary disorders		
Proteinuria	1.1%	2.7%
Urinary incontinence	0.6%	1.0%
Micturition urgency	0.6%	1.0%
Nocturia	0%	1.0%
Reproductive system and breast disorders		
Dysmenorrhea[1]	0%	2.4%
Ejaculation disorder[2]	0%	2.4%
Metrorraghia[1]	0%	1.9%
Vaginal candidiasis[1]	0%	1.4%
Impotence[2]	0%	1.2%
General disorders and administration site conditions		
Injection site reaction*	8.5%	48.3%
Influenza-like illness*	18.2%	44.2%
Asthenia	17.0%	21.6%
Pyrexia*	4.5%	13.0%
Injection site pain	2.8%	5.8%
Chills*	1.1%	5.5%
Pain	4.0%	4.1%
Gait disturbance	0.6%	2.1%
Malaise	0.6%	1.0%
Chest pain	0%	1.0%
Injection site inflammation	0%	1.0%
Injection site necrosis	0%	1.0%
Investigations		
Alanine aminotransferase increased*	4.5%	15.4%
Aspartate aminotransferase increased*	2.8%	11.0%
Liver function test abnormal*	1.1%	5.5%
Laboratory test abnormal	1.7%	2.1%
Gamma-glutamyltransferase increased	0.6%	1.0%
Injury, poisoning and procedural complications		
Injury	4.0%	5.5%
Subcutaneous hematoma	2.8%	3.4%
Post-procedural complication	0%	1.4%

*Significantly associated with BETASERON treatment ($p<0.05$).
[1] Incidence in females only (n=207).
[2] Incidence in males only (n=85).

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See our ad on pages A-10, A-11

University of Toronto - University Health Network/Mount Sinai Hospital

NEUROMUSCULAR NEUROLOGIST - Clinical Scientist

The Division of Neurology, Department of Medicine at The University Health Network/Mount Sinai Hospital (UHN/MSH) at the University of Toronto is seeking a clinician scientist with a focus in neuromuscular diseases.

The applicant must hold certification from the Royal College of Physicians and Surgeons of Canada in Neurology or be eligible for certification. The successful candidate will have fellowship training in neuromuscular disorders, including both clinical and electrodiagnositc techniques for the evaluation of peripheral neuromuscular disorders and central spinal motor control. Ideally, he or she will have experience in carrying out clinical trials in neuromuscular disorders, will have established expertise in both clinical care and teaching in neurology and will join a multidisciplinary academic neuromuscular clinic. He or she will be able to create and sustain an independent research program in the area of neuromuscular disorders and/or spinal physiology and will be expected to collaborate and interact with scientists at the University of Toronto and UHN/MSH who are pursuing molecular genetic, molecular biological, cell biological, neurophysiologic and neuroimaging research in this area, specifically in the field of spinal cord research.

The successful candidate will participate in all aspects of the UHN/MSH Neuroscience Program. He or she will be expected to participate in other clinical and research aspects of the Program of the UHN/MSH and the University of Toronto. Academic appointment in the Division of Neurology, University of Toronto and salary will be commensurate with training and experience.

The University of Toronto is strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, Aboriginal persons, persons with disabilities, members of sexual minority groups, and others who may contribute to further diversification of ideas. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority.

Please send curriculum vitae and letter of application to:

Vera Bril, BSc, MD, FRCPC
Professor of Neurology, University of Toronto, Head, Division of Neurology, UHN/MSH
University Health Network and Mount Sinai Hospital, Head,Neuromuscular Program, University of Toronto
5 Eaton Centre, 200 Elizabeth St,
Toronto, Ontario, M5G 2C4
Tel: (416) 340-3315 Fax: (416) 340-4189

University of Toronto - University Health Network/Mount Sinai Hospital

NEUROMUSCULAR NEUROLOGIST - Clinical Teacher

The Division of Neurology, Department of Medicine at The University Health Network/Mount Sinai Hospital (UHN/MSH) at the University of Toronto is seeking a clinician scientist with a focus in neuromuscular diseases.

The Division of Neurology, Department of Medicine at The University Health Network/Mount Sinai Hospital (UHN/MSH) at the University of Toronto is seeking a clinician teacher with a focus in neuromuscular diseases.

The applicant must hold certification from the Royal College of Physicians and Surgeons of Canada in Neurology or be eligible for certification. The successful candidate will have fellowship training in neuromuscular disorders, including both clinical and electrodiagnositc techniques for the evaluation of peripheral neuromuscular disorders. Ideally, he or she will have established expertise in both clinical care and teaching in neurology and will join a multidisciplinary academic neuromuscular clinic. He or she will demonstrate expertise in teaching by completing the Masters Teacher program at the University of Toronto, or equivalent credentials. He or she will be expected to collaborate and interact with other teachers at the University of Toronto and UHN/MSH to maintain the excellence of the teaching program at the University of Toronto.

The successful candidate will participate in all aspects of the UHN/MSH Neuroscience Program. He or she will be expected to participate in other clinical and research aspects of the Program of the UHN/MSH and the University of Toronto. Academic appointment in the Division of Neurology, University of Toronto and salary will be commensurate with training and experience.

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The Canadian Neurological Sciences Federation

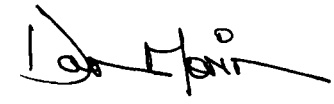
Overall Congress Evaluation

Evaluation completed June 2007

The CNSF worked very hard to ensure that delegates at the 2007 Congress filled in the Course Specific and Overall Congress Evaluations. As tools to rate relevance and satisfaction with learning objectives and perceived learning needs, the CNSF recognized that a good response rate was critical and so for the first time made receipt of delegate Maintenance of Certification certificates dependent on completion of the Overall Congress Evaluation.

The result was that 56% of attending delegates completed and submitted the evaluation. The Professional Development and Scientific Program Committees used the information from the Evaluations to construct the Congress Program for Victoria in 2008; more changes based on these results are already planned for 2009!

Some of the interesting results are included here.



Dan Morin
The Canadian Neurological Scienced Federation, CEO

Which of the following best describes your occupation?

	Response Percent
Clinical Practice	76.0%
Education or Education Administration	12.2%
Research or Admininstration of Research	14.2%
Health Care Administation	4.5%
Residency	13.4%
Other	9.4%

Please rate the RELEVANCE of each topic area offered at the 2007 Congress to your professional activities and educaitonal needs:

Of those who attended and reported	Very Relevant	Relevant	Not Relevant
Neurobiology Review Course	36%	60%	4%
Child Neurology Day	69%	29%	2%
Epilepsy Video Session	68%	32%	0%
Movement Disorders Course	81%	17%	2%
Stroke Satellite (Boehringer Ingelheim)	68%	28%	4%
Stroke Satellite (Novo Nordisk)	63%	35%	2%
MS Satellite (Biogen)	48%	50%	2%
Neuropathic Pain Course	69%	31%	0%
Spine Course	73%	24%	3%
EMG Course	83%	14%	3%
Neurocritical Care Course	67%	31%	2%
Epilepsy Course	82%	17%	1%
Stroke Course	78%	22%	0%
Neuropathic Pain Satellite (Pfizer)	47%	47%	6%
Headache Course	62%	31%	7%
What's New in Neurosurgery Course?	76%	24%	0%
EEG Course	85%	10%	5%

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Please rate the RELEVANCE of each topic area offered at the 2007 Congress to your professional activities and educaitonal needs:

Of those who attended and reported	Very Relevant	Relevant	Not Relevant
continued from page 1			
Dementia Course	52%	37%	8%
MS Course	42%	47%	11%
What's New in Neurology Course?	71%	26%	3%
Neuromuscular Course	79%	19%	2%

Educational Objectives for the 2007 Congress:

By the end of the Congress the participants will be able to:

- Discuss the advances in the diagnosis and management of acute and chronic neurological diseases
- Review new treatment options for neurosurgical illnesses
- Explore advances in neurobiology
- Assess the consequences of neurological injury in the newborn

Rate how we did in meeting these objectives:

Of those who reported (220)

	Response Percent
Very well met	35%
Met	55%
Not met	2%
Unable to comment	8%

Please rate your SATISFACTION with the following activities of the Congress:

Of those who attended and reported	Very Satisfied	Satisfied	Dissatisfied
Welcome Reception	38%	57%	5%
Presidents' Reception	45%	49%	6%
Presidents' Dinner	60%	37%	3%
Grand Opening Plenary	73%	27%	0%
Plenary-CNS Neurology	64%	30%	6%

Please rate your SATISFACTION with the following activities of the Congress:

Of those who attended and reported	Very Satisfied	Satisfied	Dissatisfied
Plenary-CNSS Neurosurgery	73%	27%	0%
Plenary-Distinguished Guest Lecturer	79%	16%	5%
Combined Platform Sessions	60%	38%	2%
Platform Sessions	51%	46%	3%
Feature Courses	65%	34%	1%
Satellite Symposia	48%	51%	1%
Digital Poster Presentations	25%	40%	35%
Grand Rounds	71%	28%	1%
Exhibits	27%	61%	12%

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Please rate your SATISFACTION with the following elements of the Congress:

Of those who attended and reported	Very Satisfied	Satisfied	Dissatisfied
Diversity of Topics	39% (85)	60% (132)	1% (3)
Numbers of Topics Offered	37% (80)	61% (135)	2% (5)
Session Mix (i.e. plenary, courses, workshops etc.)	36% (80)	61% (134)	3% (6)
Peer Networking	39% (86)	57% (126)	4% (8)
Pre-Congress Information	26% (58)	66% (145)	8% (17)
Congress Program	26% (57)	64% (141)	10% (22)
Congress Materials Provided on CD	26% (57)	61% (133)	14% (30)
Conference Location and Facilities	34% (75)	57% (126)	9% (19)
Quality of Presentations	42% (92)	57% (125)	1% (3)

How much did the following contribute to your decision to attend the Congress?

Of those who attended and reported	Greatly Contributed	Contributed	Did not contribute
Overall Program Content	24% (53)	66% (145)	10% (22)
Reviewing or Developing Clinical Skills	21% (47)	53% (116)	26% (57)
Administrative or Society Meetings	20% (44)	36% (80)	44% (96)
Ability to Network with Peers	41% (89)	43% (96)	16% (35)
Social Opportunities	20% (43)	48% (107)	32% (70)
Destination Appeal	15% (33)	36% (80)	49% (107)
Keeping Abreast of New Developments	35% (77)	52% (114)	13% (29)
Close Proximity to Personal Residence	16% (35)	23% (50)	61% (135)

What is your overall rating for the Congress?

Of those who reported (220)

	Response Percent
Very good	41%
Good	55%
Poor	4%

Do you plan to attend?

Of those who reported (220)

	Do Not Know	Definately	No
Victoria, BC June 17-20, 2008	48% (105)	49% (107)	3% (8)
Future Congresses?	42% (93)	57% (126)	1% (1)

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Patient Selection Criteria

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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.

Safety Information

WARNINGS AND PRECAUTIONS

(see Supplemental Product Information for full listing)

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 adversely affect them.

Cardiovascular

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

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

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

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

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

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

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

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

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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, 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.

(1109-a,11,07)

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THE CNSF CELEBRATES ITS

60TH

ANNIVERSARY IN 2008!

The Canadian Neurological Association was established in 1948. The founding meeting was held in Montreal and was attended by Wilder Penfield, Allan Waters, Walter Hyland, Jean Saucier, Francis McNaughton and Roma Amyot.

The first general meeting of the Association was held at the Royal York Hotel in Toronto and was attended by 38 prospective members from across the country. The Association was established to represent neurology, neurosurgery and neurobiology and Dr. Wilder Penfield was named first president. In 1949, the Association was renamed the Canadian Neurological Society.

In 1965, the Canadian Neurological Society, representing both neurologists and neurosurgeons, was dissolved and two new Societies were formed representing two distinct disciplines – the new Canadian Neurological Society for neurologists and the Canadian Neurosurgical Society for neurosurgeons. A liaison committee, with executive officers from the two Societies, was formed to administer conjoint activities. This committee was important in planning the first annual joint meeting held in 1965 – the first Canadian Congress of Neurological Sciences.

In subsequent years, the two Societies were joined by the Canadian EEG Society (later named the Canadian Society of Clinical Neurophysiologists) and the Canadian Association of Child Neurology.

In 1990, the Canadian Congress of Neurological Sciences was formally incorporated with a Board of Directors representing each of the four member Societies, with a permanent Secretariat Office in Calgary. In 2006, the name was changed to the Canadian Neurological Sciences Federation (CNSF).

The CNSF Today

This unique partnership of neurologists, neurosurgeons, clinical neurophysiologists and child neurologists continues to hold a combined annual Congress in June every year. Additionally, the CNSF now publishes the Canadian Journal of Neurological Sciences, the 'Journal'.

A Board of Directors governs the CNSF. The Board consists of two members (the President and Vice President) from each of the four Societies, the President and two Vice-Presidents of the Board who are appointed from the general membership of the four Societies, one Neurology or Neurosurgery resident (alternating), the immediate Past-Chair of the Board (non-voting), and the CNSF CEO (non-voting).

The CNSF has approximately 1,100 members and eight full-time staff in the Secretariat Head Office.

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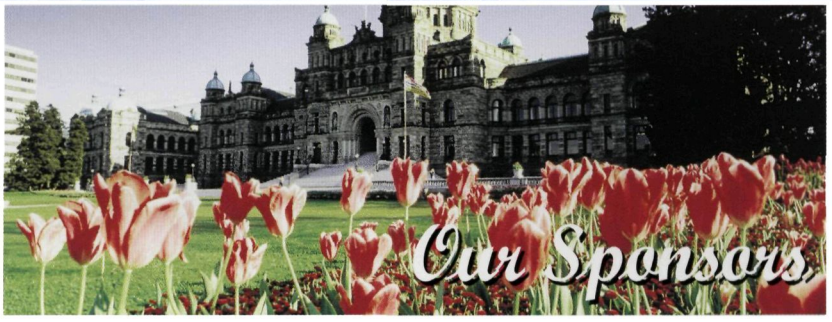

The Canadian Neurological Sciences Federation is pleased to recognize our Sponsors* for 2008. These organizations partner with CNSF to determine the causes of, and develop treatment for diseases and injuries of the nervous system, and in the care of patients with these diseases and injuries. Along with support of the Canadian Journal of Neurological Sciences and other initiatives the CNSF maintains throughout the year, these organizations graciously provide unrestricted educational grants to the Annual Congress, this year in Victoria, British Columbia; June 17th – 20, 2008.

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Teva Neuroscience
Karl Storz

IMRIS
Neurologica
Bayer Healthcare

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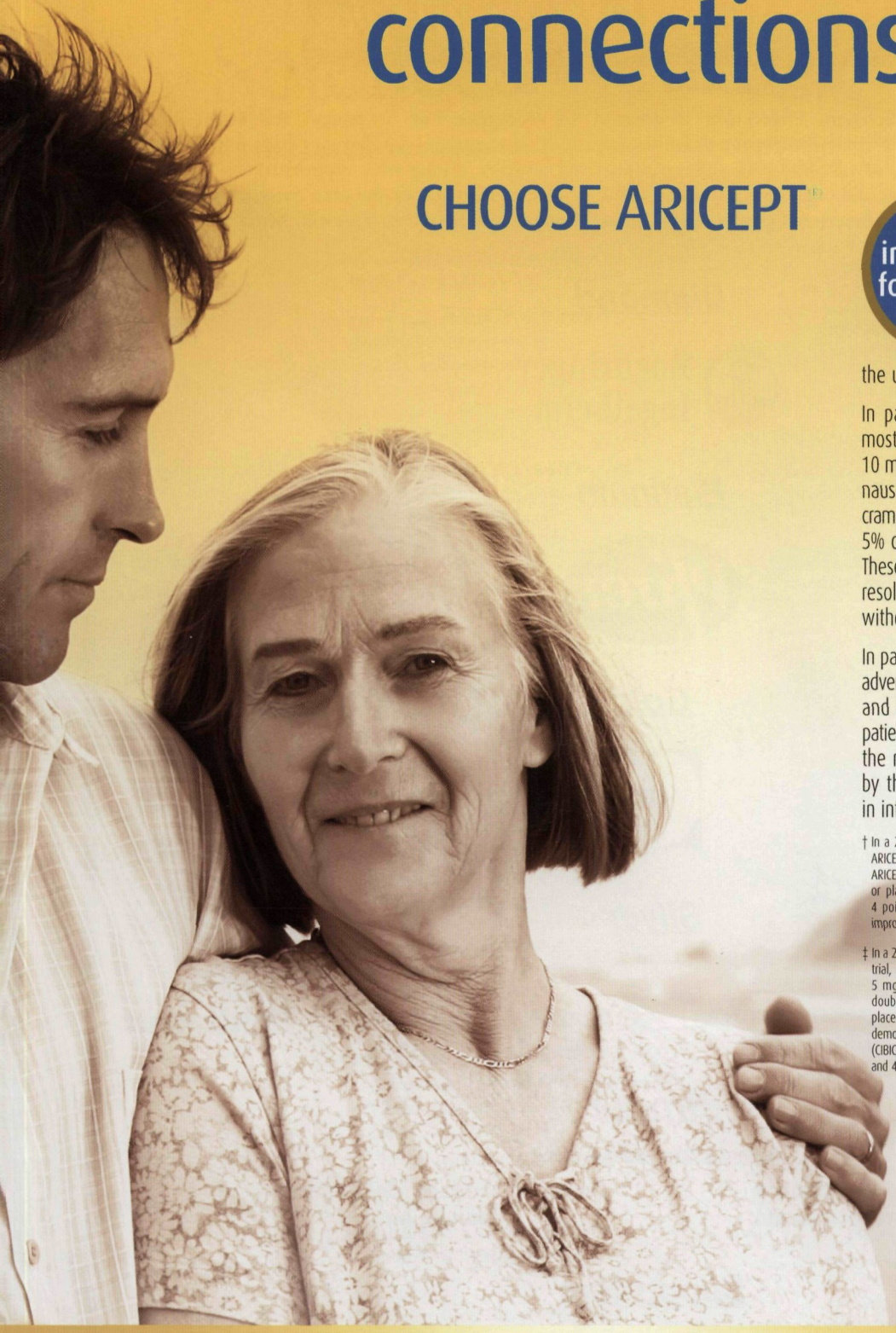
Helping her make connections[1,2†‡]



CHOOSE ARICEPT®

Now indicated for severe AD

ARICEPT is indicated for the symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type. ARICEPT does not change the underlying course of the disease.

In patients with mild-to-moderate AD, the most common adverse events with ARICEPT 10 mg/d after proper dose escalation include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia (occurring in at least 5% of patients and at twice the placebo rate). These events are usually mild and transient, resolving with continued ARICEPT treatment without the need for dose modification.

In patients with severe AD, the most common adverse events were vomiting, diarrhea, nausea, and aggression (occurring in at least 5% of patients and at twice the placebo rate). Overall, the majority of adverse events were judged by the investigators to be mild or moderate in intensity.

† In a 24-week, randomized, double-blind, placebo-controlled study of ARICEPT in 153 mild AD patients (MMSE 21-26). Patients received either ARICEPT 5 mg/d for the first 6 weeks and 10 mg/d thereafter, (n=96), or placebo (n=57). 37% of ARICEPT-treated patients experienced a 4 point ADAS-cog improvement and 10% experienced a 7 point improvement vs. 16% and 7% respectively with placebo.

‡ In a 24-week, multicentre, randomized, double-blind, placebo-controlled trial, 473 patients (MMSE 10-26) were randomized to receive ARICEPT 5 mg/d, ARICEPT 10 mg/d or placebo. Following the 24-week, double-blind phase, all patients underwent a 6-week, single-blind placebo washout. Patients treated with either dose of ARICEPT demonstrated significantly less decline on the CIBIC-plus vs. placebo (CIBIC-plus values at endpoint for ARICEPT 5 mg/d and 10 mg/d were 4.15 and 4.07 respectively vs. 4.51 with placebo, p=0.0047 and p<0.0001).

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First Alzheimer's Therapy in Canada

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See prescribing summary on page A-21-A-24