Volume 29 Number 1 February 2002

THE CANADIAN JOURNAL OF Neurological Sciences

LE JOURNAL CANADIEN DES Sciences Neurologiques

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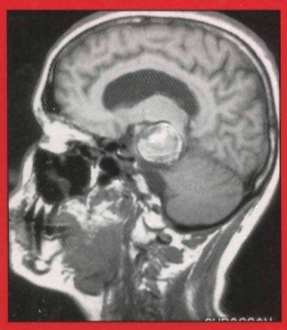
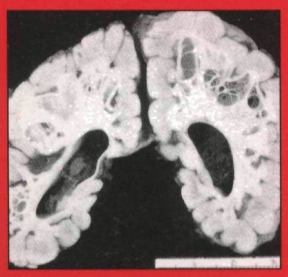


Non-Atherosclerotic Fusiform Cerebral Aneurysms



Honeycombing of the white matter

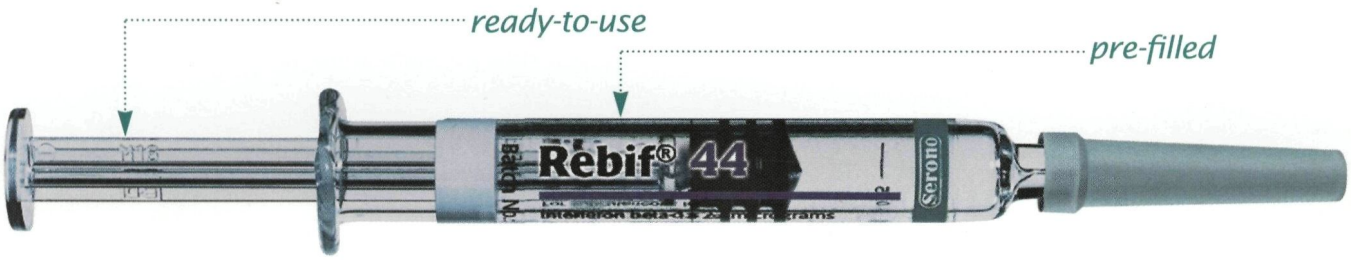
37th CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES
June 18 - 22, 2002
Vancouver, British Columbia

The official Journal of: The Canadian Neurological Society, The Canadian Neurosurgical Society, The Canadian Society of Clinical Neurophysiologists, The Canadian Association of Child Neurology

Rebif®. Dose-dependent Efficacy in Relapsing MS[1]*.

Pr Rebif®

Interferon beta-1a



The most common reported adverse events are injection-site reactions and flu-like symptoms – e.g., asthenia, pyrexia, chills, arthralgia, myalgia, and headache. These tend to decrease in frequency and severity with continued treatment. Please see product monograph for full prescribing information. Evidence of safety and efficacy derived from 2-year data only.

* Rebif® is indicated for the treatment of relapsing-remitting multiple sclerosis in patients with an EDSS between 0 and 5.0, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids, and reduce the number of hospitalizations for treatment of multiple sclerosis.

REFERENCES:

[1] PRISMS (Prevention of Relapses and Disability by Interferon ß-1a Subcutaneously in Multiple Sclerosis) Study Group (1998). Randomised double-blind placebo-controlled study of interferon ß-1a in relapsing/remitting multiple sclerosis. Lancet 352:1498-1504

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IF YOU STARTED PATIENTS ON REQUIP, WOULD THE FUTURE LOOK DIFFERENT?

Interim 6-month results from a 5 year multicentre study show ReQuip demonstrated similar efficacy to L-dopa in the control of early† Parkinson's disease.[1††] Yet ReQuip ropinirole REQUIP® Rethinking Parkinson's. has demonstrated a low propensity to produce dyskinesias.[2†††] Maybe it's time to rethink Parkinson's. And start early Parkinson's patients on ReQuip alone.

† Hoehn and Yahr stages I-II †† A 6 month interim analysis of a 5-year, double-blinded, randomized, multicenter study of patients with early Parkinson's disease. N = 268:179 patients received ropinirole and 89 received L-dopa. The mean daily dose was 9.7 mg and 464.0 mg respectively. There was no difference in Clinical Global Improvement scale in patients with Hoehn and Yahr stages I-II although L-dopa showed improvement in a greater proportion of patients with more severe disease. The proportion of responders was 58% in the L-dopa group and 48% in the ropinirole group: this was not of statistical significance. ††† In early therapy, the respective incidences of dyskinesia in early therapy of patients receiving ropinirole was 1.2% and of patients receiving L-dopa was 11.2%. Meta analysis, n = 1364, 17 months. Nausea (39.1%), somnolence (12.3%) and insomnia (12.3%) were the most common side effects of ReQuip therapy. Six percent of ropinirole patients and nine percent of L-dopa patients had at least one psychiatric symptom (confusion, hallucinations, or delusions).

Member PAAB R&D

gsk GlaxoSmithKline

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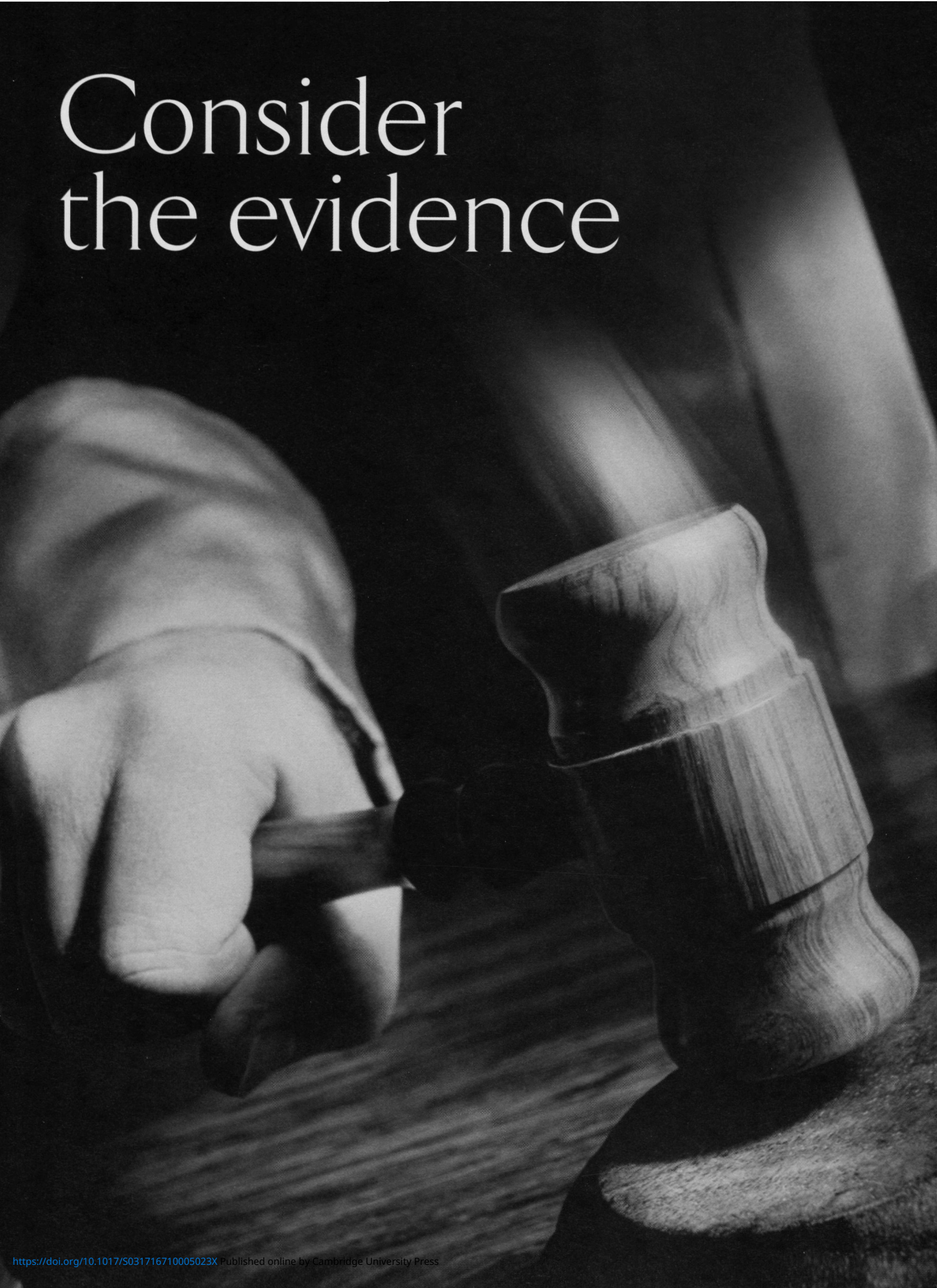

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AVONEX® is proven effective in Relapsing Remitting MS

- 37% reduction in the probability of disability progression over two years (21.9% vs. 34.9%; p=0.02)[¶1,2]
- 32% reduction in the annual exacerbation rate over two years (0.61 vs. 0.90; p=0.002)[*1,2]
- 38% of patients remained relapse free at two years (p=0.03)[@1,2]
- 55% reduction in brain atrophy progression during the second year of therapy (-0.233 vs. -0.521; p=0.03)[#3]
- 89% reduction in gadolinium-enhanced lesions in patients with enhancement at baseline (0.11 vs. 0.50; p=0.041)[†4]
- AVONEX® is indicated for the treatment of relapsing forms of MS.[1]

AVONEX® is generally well tolerated. The most common side effects associated with treatment are flu-like symptoms (muscle ache [myalgia], fever, chills, and asthenia). Please see product monograph for important patient selection and monitoring information.[1] AVONEX® should be used with caution in patients with depression and in patients with seizure disorders. AVONEX® should not be used by pregnant women. Patients with cardiac disease should be closely monitored. Routine periodic blood chemistry and hematology tests are recommended during treatment with AVONEX®.[1]

P ONCE-A-WEEK
AVONEX®
(Interferon beta-1a)
IM Injection

¶ Kaplan-Meier methodology. AVONEX® n=158, placebo n=143.
* AVONEX® n=85, placebo n=87.
@ n=85.
# As measured by brain parenchymal fraction in the second year of treatment. AVONEX® n=68, placebo n=72.
† AVONEX® n=44, placebo n=44. The exact relationship between MRI findings and clinical status is unknown.

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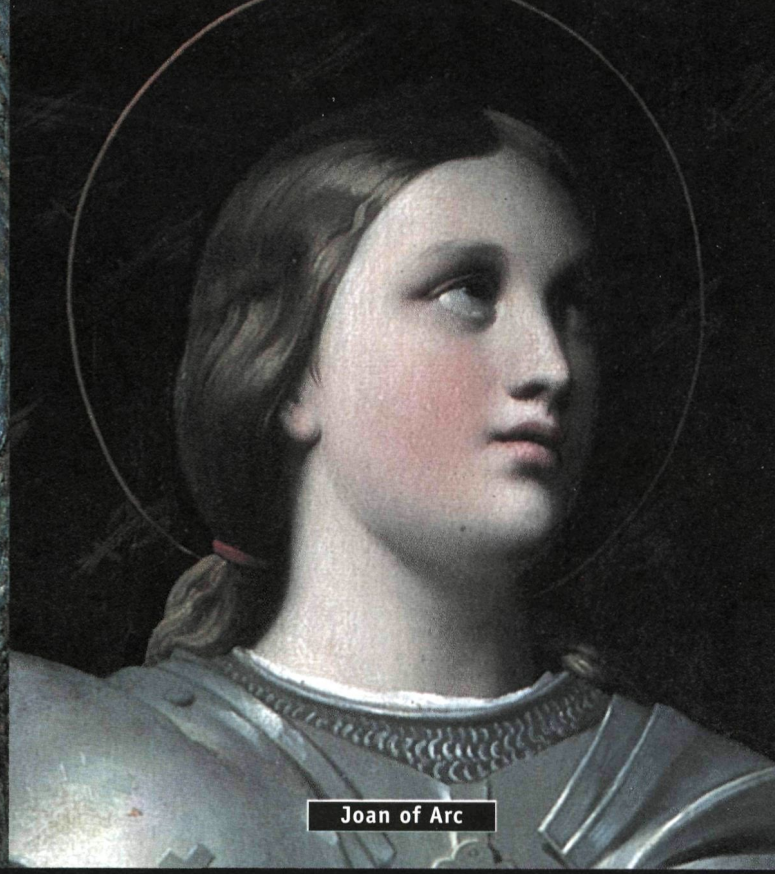
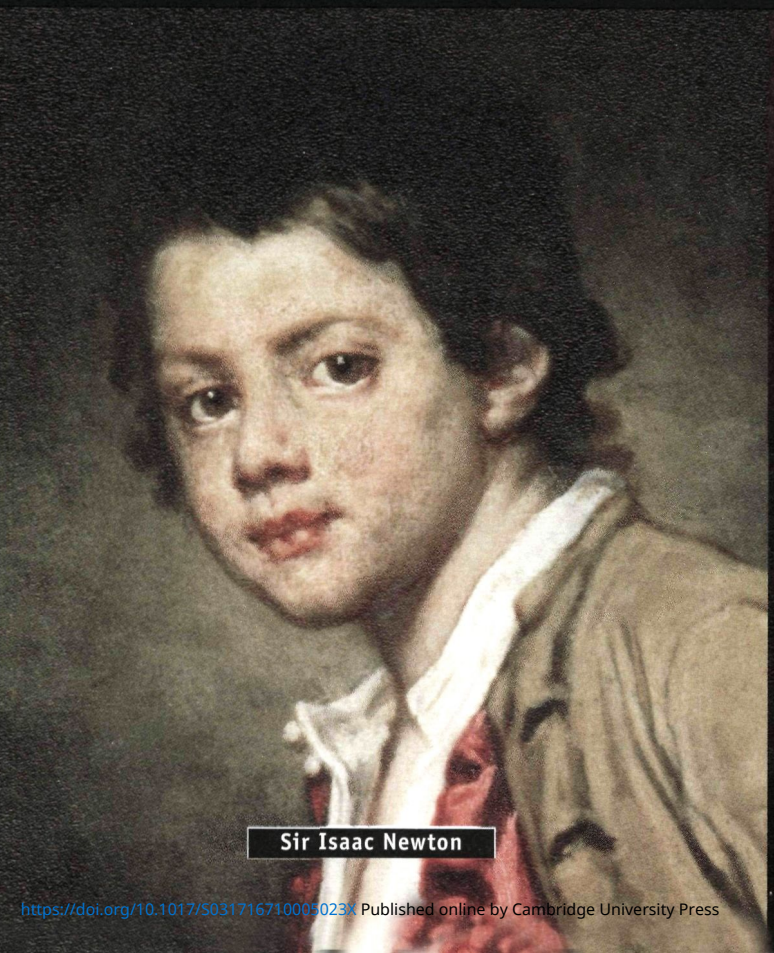
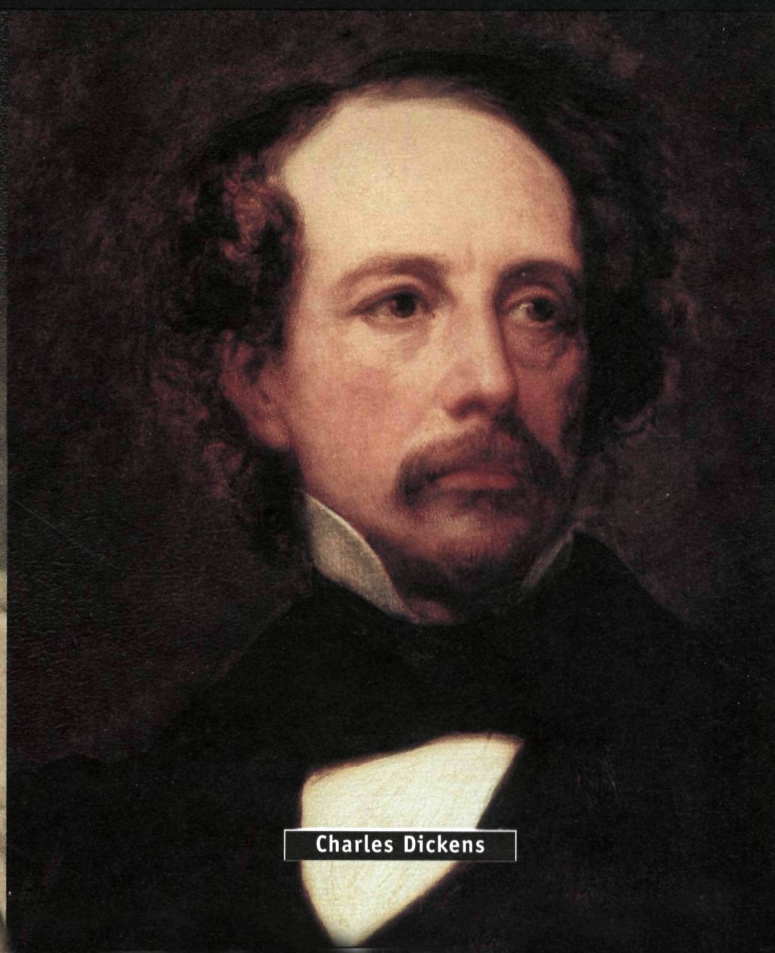


YESTERDAY, PEOPLE WITH EPILEPSY HAD TO BE EXTRAORDINARY TO SUCCEED.





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EFFICACY ACROSS A BROAD RANGE OF SEIZURES.

- TOPAMAX demonstrates efficacy in Partial Onset, Primary Generalized Tonic-Clonic, and Lennox-Gastaut Seizures[1]
- Desirable seizure-free results were shown in both Adults (19%)† and Children (22%)‡ with Partial Onset Seizures[2,3]

NO EVIDENCE OF LIFE-THREATENING SIDE EFFECTS.

- Like most antiepileptics, the most common side effects are CNS related, usually mild to moderate and transient§[1]

ADULT PATIENTS MAY EXPERIENCE WEIGHT LOSS.

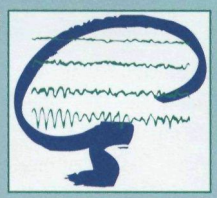
- 73% of patients (n=52) showed a mean weight decrease of 5.97 lb (Interim analysis. Average duration 60 days)[4]
- 96% of children in clinical trials (≥ one year) who lost weight showed resumption of weight gain in test period**[1]

TODAY, THERE'S TOPAMAX.

B.I.D. DOSING WITH THE PATIENT IN MIND.

- TOPAMAX is initiated and titrated to clinical response regardless of existing anticonvulsant therapy
- Tablets available on formulary††

NOW AVAILABLE IN SPRINKLE CAPSULES



TOPAMAX* topiramate

NOW INDICATED FOR CHILDREN

HELPING PATIENTS MAKE MORE OF THEIR LIVES.

Pr TOPAMAX topiramate Tablets and Sprinkle Capsules: indicated as adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy who are not satisfactorily controlled with conventional therapy. There is limited information on the use of topiramate in monotherapy at this time.*

† Open label, 20 week trial (n=450 Adults). Optimal dosing was 300-350 mg/day(Average 288 mg/day).
‡ Open label trial for children (n=72) treated for ≥ 3 months. Average dose of 10 mg/kg/day.
§ CNS adverse events: Somnolence (30.1%), dizziness (28.3%), ataxia (21.2%), speech disorders (16.8%), psychomotor slowing (16.8%), nystagmus (15.0%), paresthesia (15.0%), nervousness (15.9%), difficulty with concentration/attention (8.0%), confusion (9.7%), depression (8.0%), anorexia (5.3%), language problems (6.2%) and mood problems (3.5%). In an audit of 1446 adults and 303 children, there appeared to be a similar pattern of adverse events.
** The long-term effects of weight loss in pediatric patients are not known.
†† Limited use benefit: Ontario, Nova Scotia, New Brunswick, PEI. Full benefit: Quebec, Saskatchewan, British Columbia, Alberta, Manitoba.
Please refer to the TOPAMAX Prescribing Information for complete prescribing details.

REFERENCES: 1. TOPAMAX* topiramate Tablets and Sprinkle Capsules Product Monograph, May 11, 1999. 2. Kamin M, Kraut L, Olson W. Dose optimization of topiramate as add-on therapy in adults with treatment-resistant partial-onset seizures *Neurology* 1999;52 (Suppl 2):A525-526. 3. Glauser TA, Elterman R, Wyllie E et al. Open label topiramate in paediatric partial epilepsy *Epilepsia* 1997:38 (Suppl 3):94. 4. Rosenfeld WE et al.Topiramate and concomitant weight loss. *Epilepsia* 1997:38 (Suppl 8):98.

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• Submit five high quality copies of the manuscript and original illustrations. Papers will be accepted in English or French. Manuscripts must be double spaced throughout including references, tables and legends for illustrations. Margins of at least 25mm should be left on all sides.

• After a paper has been reviewed, the author will be requested to submit four copies of the revised manuscript, including illustrations. Supply a computer diskette (3 1/2" size) containing the article *saved in an RTF format*. Identify clearly first author's name, file name, word processing program and version, and system (i.e. PC or Mac). Clearly indicate the order and importance of headings.

• For detailed instructions regarding style and layout refer to *"Uniform requirements for manuscripts submitted to biomedical journals"*. Copies of this document may be obtained by writing to the Journal office, but the main points are summarized here. Articles should be submitted under conventional headings of *introduction, methods and materials, results, discussion,* but other headings will be considered if more suitable. Clinical trials must be reported in Consort format (JAMA 1996; 276: 637-639). Pages of text should be numbered consecutively.

• ***A title page*** should identify the title of the article which should be no more than 80 characters including spaces; name of institution(s) from which the work originated; and the name, address, telephone, and fax number of the corresponding author.

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Journals

Yang JF, Fung M, Edamura R, et al. H-Reflex modulation during walking in spastic paretic subjects. Can J Neurol Sci 1991; 18: 443-452.

Chapter in a book

McGeer PL, McGeer EG. Amino acid neurotransmitters. *In*: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. Basic Neurochemistry. Boston: Little, Brown & Co., 1981: 233-254.

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Once-a-day Aricept*

donepezil HCl 5 & 10 mg tablets

PHARMACOLOGIC CLASSIFICATION Cholinesterase Inhibitor **ACTION AND CLINICAL PHARMACOLOGY ARICEPT** (donepezil hydrochloride) is a piperidine-based, reversible inhibitor of the enzyme acetylcholinesterase. A consistent pathological change in Alzheimer's disease is the degeneration of cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. The resulting hypofunction of these pathways is thought to account for some of the clinical manifestations of dementia. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine (ACh) through reversible inhibition of its hydrolysis by acetylcholinesterase (AchE). If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process. **INDICATIONS AND CLINICAL USE ARICEPT** (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. **ARICEPT** tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. **CONTRAINDICATIONS ARICEPT** (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS *Anaesthesia:*** **ARICEPT** (donepezil hydrochloride), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia. ***Neurological Conditions: 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 Alzheimer's disease. 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 moderately severe or severe Alzheimer's disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patient populations is unknown. ***Pulmonary Conditions:*** 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. ***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, 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 Alzheimer's disease, 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 one -to- three 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. **PRECAUTIONS *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. ***Use in Patients ≥65 Years Old:*** In controlled clinical studies with 5 and 10 mg of **ARICEPT**, 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's disease 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 Alzheimer's disease 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 Alzheimer's disease and significant comorbidity. The use of **ARICEPT** in Alzheimer's disease 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. Caution is advised regarding the use of **ARICEPT** doses above 5 mg in this patient population. ***Renally and Hepatically Impaired:*** There is limited information regarding the pharmacokinetics of **ARICEPT** in renally and hepatically impaired Alzheimer's disease patients. Close monitoring for adverse effects in Alzheimer's disease patients with renal or hepatic disease being treated with **ARICEPT** is therefore recommended. ***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. ***Drugs Highly Bound to Plasma Protein:*** 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 5mg/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 CYP 450, 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. ***Use in Pregnancy and Nursing Mothers:*** 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. 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**. ***Pediatric Use:*** 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. **ADVERSE REACTIONS** A total of 747 patients with mild-to-moderate Alzheimer's disease 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). ***Adverse Events Leading to Discontinuation:*** The rates of discontinuation from controlled clinical trials of **ARICEPT** due to adverse events 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%. The most common adverse events 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 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%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT: The most common adverse events, 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 cramps, fatigue and anorexia. These adverse events 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 adverse events may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day. 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 adverse events were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a one-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 adverse events following one- and six-week initial treatment periods with 5 mg/day **ARICEPT**.

Table 2. Comparison of Rates of Adverse Events in Patients Treated with 10 mg/day after 1 and 6 Weeks of Initial Treatment with 5 mg/day

	No Initial Treatment		One-Week Initial Treatment with 5 mg/day	Six-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%

Adverse Events Reported in Controlled Trials: The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 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, adverse events occurred more frequently in female patients and with advancing age.

Table 3. 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	Body System/ Adverse Events	Placebo n = 355	ARICEPT n = 747
Percent of Patients with any Adverse Event	72	74	**Metabolic and Nutritional**		
Body as a Whole			Weight Decrease	1	3
Headache	9	10	**Musculoskeletal System**		
Pain, various locations	8	9	Muscle Cramps	2	6
Accident	6	7	Arthritis	1	2
Fatigue	3	5	**Nervous System**		
Cardiovascular System			Insomnia	6	9
Syncope	1	2	Dizziness	6	8
Digestive System			Depression	<1	3
Nausea	6	11	Abnormal Dreams	0	3
Diarrhea	5	10	Somnolence	<1	2
Vomiting	3	5	**Urogenital**		
Anorexia	2	4	Frequent Urination	1	2
Hemic and Lymphatic Systems					
Ecchymosis	3	4			

Other Adverse Events Observed During Clinical Trials: During the pre-marketing phase, **ARICEPT** has been administered to over 1700 individuals 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 three placebo-controlled clinical trials and two open-label trials were recorded as adverse events 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 who experienced that event while receiving **ARICEPT**. All adverse events occurring at least twice are included. Adverse events 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 adverse events 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. **Adverse Events Occurring in ≥1% and <2% or <1% of Patients Receiving ARICEPT:** ***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%) faecal 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, haemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. ***Endocrine System:*** (<1%) diabetes mellitus, goiter. ***Hemic & Lymphatic System:*** (<1%) anaemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. ***Metabolic and 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:*** Patients were exposed to **ARICEPT** in two open-label extension studies (n=985) of over two years. In one of the studies, 763 patients who previously completed one of two 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 one and two years of treatment, 78% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative weeks 48 and 108). ***Postmarketing Reports:*** Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hypoandremia, pancreatitis, and rash. **DOSAGE AND ADMINISTRATION *ARICEPT*** (donepezil hydrochloride) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. The recommended initial dose of **ARICEPT** 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. For those patients who do not respond adequately to the 5 mg daily dose after 4 -to- 6 weeks of treatment, the 10 mg daily dose may then be considered. The maximum recommended dose is 10 mg taken once daily. Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. Adverse events are more common in individuals of low body weight, in patients ≥ 85 years old and in females. It is recommended that **ARICEPT** be used with caution in elderly women of low body weight and that the dose should not exceed 5 mg/day. **ARICEPT** should be taken once daily in the evening, before retiring. For patients experiencing insomnia, **ARICEPT** may be taken in the morning. It may be taken with or without food. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision. **AVAILABILITY OF DOSAGE FORMS ARICEPT** is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT** is available in high density polyethylene (HDPE) bottles of 30 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets). **REFERENCES:** 1. Aricept® Product Monograph. Pfizer Canada Inc., May 2000. 2. Burns A et al. Donepezil provides long-term clinical benefits for patients with Alzheimer's disease. *J Neurol* 2000;247(suppl 3):135, 539. 3. Patterson C et al. The recognition, assessment and management of dementing disorders: Conclusions from the Canadian Consensus Conference on Dementia. *CMAJ* 1999;160(suppl 12):S1-S15.

Product Monograph available upon request.

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See page A-11

Now we can celebrate the long-term benefits in the treatment of Alzheimer's disease

with once-a-day Aricept*.

There's cause for celebration—because Aricept* has been shown to result in improvement or stabilization in 80% of Alzheimer's disease patients over 6 months of treatment.[1‡] And long-term data shows that Aricept*-treated patients continued to show treatment benefits up to 3 years on cognition and global functioning compared to data expected from untreated patients.[2§] What's more, Aricept* has demonstrated long-term safety and tolerability profiles.[2†] All of which means there's even more reason to make Aricept* your standard of care.[3]

Aricept* does not change the underlying course of the disease. Aricept* is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type.

† With appropriate dose escalation 5 mg/day dose, 10 mg/day dose and placebo were shown to have comparable adverse events. Most common adverse clinical events with Aricept*: diarrhea, nausea, insomnia, fatigue, vomiting, muscle cramps and anorexia. These events are usually mild and transient, resolving with continued Aricept* treatment without need for dose modification.

‡ In a 24-week, double-blind, placebo-controlled study, 473 mild-to-moderate AD patients were randomized to receive Aricept* 5 mg/day, 10 mg/day or placebo. The mean difference for Aricept*-treated patients (10 mg/day) vs. placebo was –2.87 ± 0.63 ($p<0.0001$) units in ADAS-cog, 0.47 ± 0.11 ($p<0.0001$) units in CIBIC-plus, and 0.59 ± 0.17 ($p=0.0007$) units in CDR-SB.

§ In a 162-week, multicentre, open-label extension study, 579 patients who had previously completed a randomized, double-blind, placebo-controlled study with Aricept* were treated with Aricept* 5 mg which could be increased to 10 mg between weeks 6 and 24, as per clinician's judgement. At study endpoint, ADAS-cog declined 15.57 points (95% CI,12,19.2) vs. the estimated decline of 6-12 points per year in untreated patients.

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For brief prescribing information see page A-10

25 Years Ago in the Canadian Journal of Neurological Sciences

Quebec Cooperative Study of Friedreich's Ataxia

Phase One: A Prospective Survey of 50 Cases

Organized and Edited by André Barbeau

Cardiological Signs and Symptoms in Friedreich's Ataxia

M. Cote, A. Davignon, K. Pecko-Drouin, A. Solignac, G. Geoffroy, B. Lemieux and A. Barbeau

SUMMARY: The cardiovascular signs and symptoms were recorded in 36 patients with typical Friedreich's ataxia (Group Ia, Ib). Seventeen patients were asymptomatic and this did not correlate with the severity of the disease. No pathognomonic clinical constellation was found to reveal the underlying cardiomyopathy.

Can. J. Neurol. Sci. 1976;4:319

Electrocardiographic and Vectocardiographic Findings in Friedreich's Ataxia

S. Malo, Y. Latour, M. Cote, G. Geoffroy, B. Lemieux and A. Barbeau

SUMMARY: Electrocardiographic and vectocardiographic changes are frequent in Friedreich's ataxia. In one of 35 patients both tests were normal. The vectocardiogram is more explicit in demonstrating the severity of the QRS changes with a right ventricular hypertrophy pattern present in 60% of cases. Serial examination and ECG tracings are recommended to monitor the cardiomyopathy in this progressive neurological disorder, in order to detect the onset o congestive heart failure, significant tachyarrythmias, or obstructive cardiomyopathy.

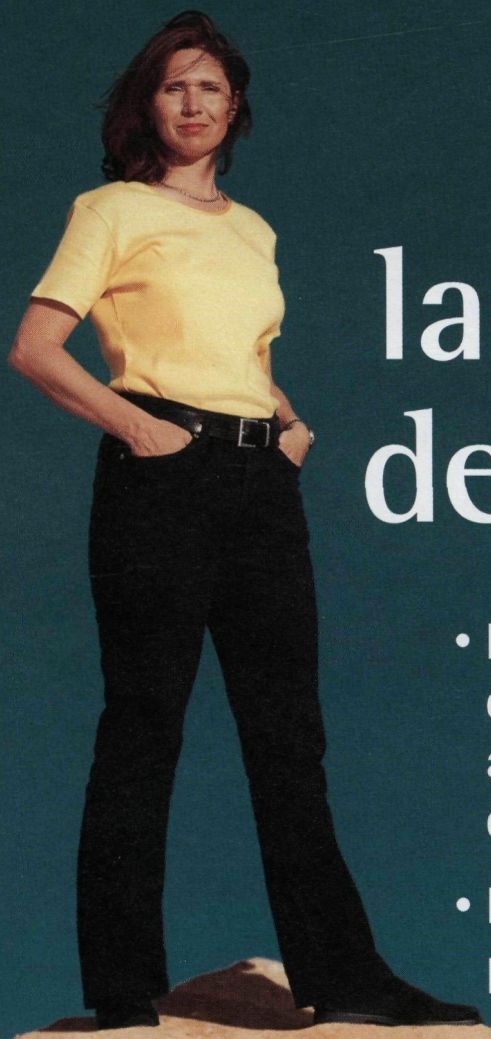
Can. J. Neurol. Sci. 1976;4:323

Echocardiographic Findings in Friedreich's Ataxia

H.F. Gattiker, A. Davignon, A. Bozio, J. Batlle-Diaz, G. Geoffroy, B. Lemieux and A. Barbeau

SUMMARY: Echocardiographic examination of 21 patients with Friedreich's ataxia (age 7 to 28 years) showed cardiac abnormalities in 90% of the cases. They were characterized by varying degrees of septal hypertrophy in 81%, left ventricular free wall hypertrophy in 61%, and a slight reduction of left ventricular internal dimension in 57% of the cases. Asymmetric septal hypertrophy (ASH) with a septal/left ventricular free wall ratio of over 1.3 was found in 29% of the cases and systolic anterior motion (SAM) of the mitral valve in three patients. Two other patients showed evidence of a different type of cardiomyopathy with marked symmetric left ventricular hypertrophy and marked left ventricular enlargement.

Can. J. Neurol. Sci. 1976;4:329



Retarde la progression de l'incapacité*[1]

- Réduit la fréquence et la gravité des poussées chez les patients atteints de SEP rémittente et de SEP progressive-secondaire[1-3]
- Effets indésirables pouvant être pris en charge†[1]

*Il a été démontré que BETASERON retarde la progression de l'incapacité chez les patients atteints de SEP progressive-secondaire[1].

L'efficacité et l'innocuité de BETASERON dans la SEP progressive-primaire n'ont pas été évaluées. On ne dispose pas de données probantes sur l'efficacité du traitement dans la SEP rémittente au-delà de deux ans, ni de données sur l'efficacité et l'innocuité du traitement dans la SEP progressive-secondaire au-delà de trois ans.

†Chez les patients atteints de SEP progressive-secondaire, les effets indésirables les plus fréquents de BETASERON sont : syndrome pseudo-grippal (61 %); fièvre (40 %); frissons (23 %); inflammation au point d'injection (48 %); réactions au point d'injection (46 %); myalgie (23 %); hypertonie (41 %) et éruption cutanée (20 %)[1]. Les symptômes pseudo-grippaux et les réactions au point d'injection peuvent être pris en charge et diminuent de façon marquée avec le temps[1].

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Pour documentation voir pages A-28, A-29

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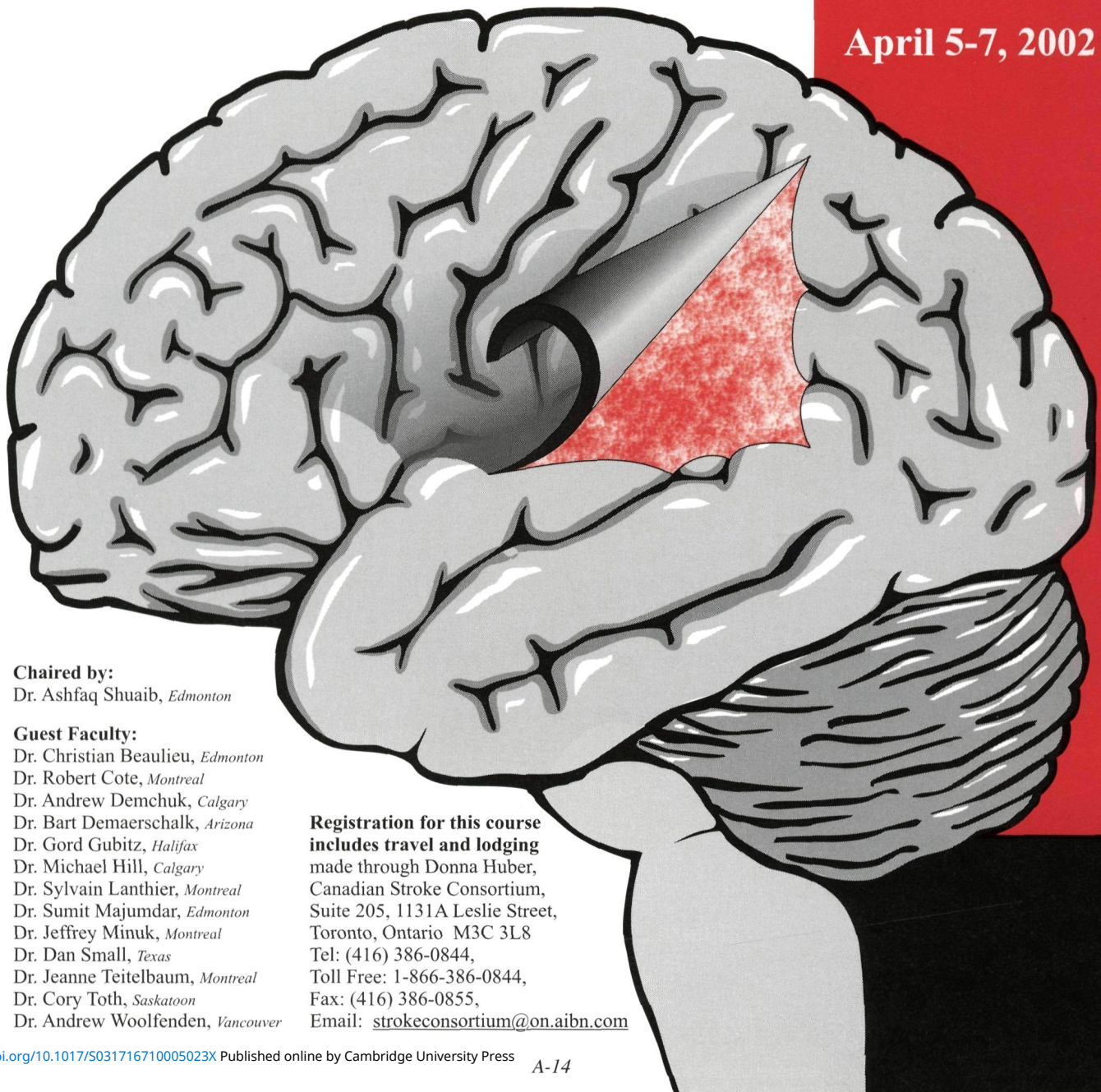

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Friday, April 5, 2002

12:00	13:00	Welcome Luncheon
13:00	13:45	Pathogenesis of Atherosclerosis
13:45	14:30	Thrombosis: role of platelets and factors
14:30	15:00	Discussion
15:00	15:15	Coffee Break
15:15	16:30	Mechanisms of Cerebral Ischemia
16:30	17:00	Imaging of early Cerebral Ischemia
17:00	17:45	Discussion
18:30		Dinner
19:30	20:15	Medical strategies to reduce the risk of ischemic stroke
20:15	21:00	High Risk Primary Prevention

Saturday, April 6, 2002

07:00	08:00	Breakfast
08:00	08:45	Evaluation and Management of TIA's
08:45	09:15	Epidemiological aspects of Stroke Prevention Clinical Trials
09:15	10:00	Antithrombotic therapy
10:00	10:30	Discussion
10:30	10:45	Coffee Break
10:45	11:30	Rapid ER evaluation of acute stroke, role of neurovascular imaging
11:30	12:15	Current treatment and new frontier
12:15	13:00	Discussion
13:00	17:30	Free Time
17:30		Reception and Dinner

Sunday, April 7, 2002

07:00	07:45	Breakfast
07:45	08:30	Complications of Acute Stroke
08:30	09:00	Discussion
09:00	12:00	Workshops: Acute Stroke Stroke Prevention Unusual Cases in Stroke

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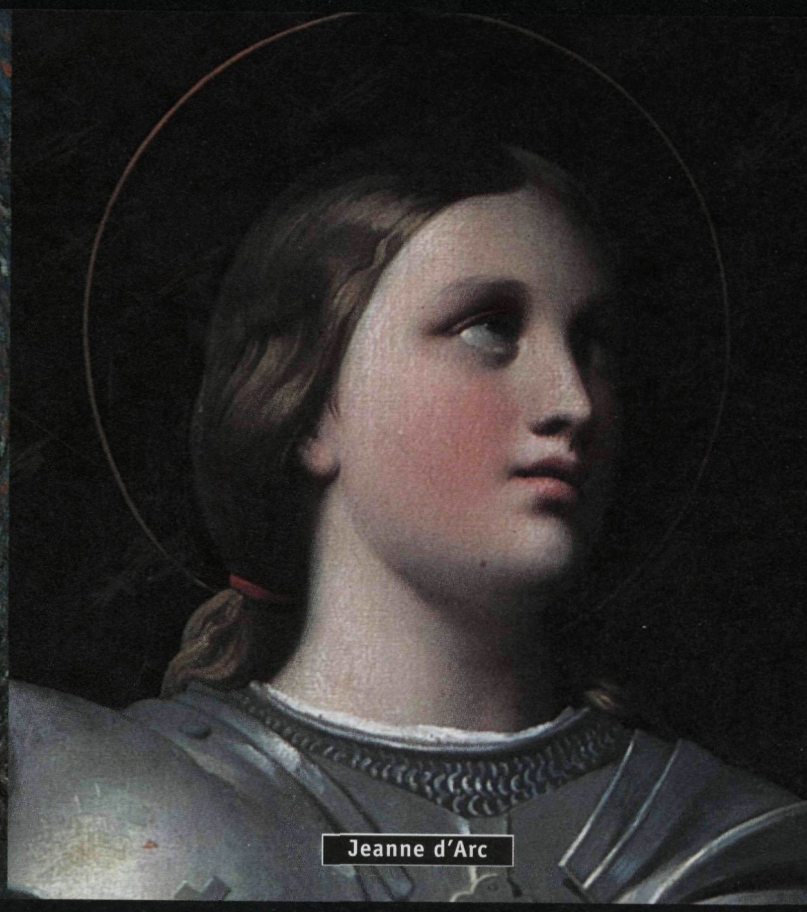
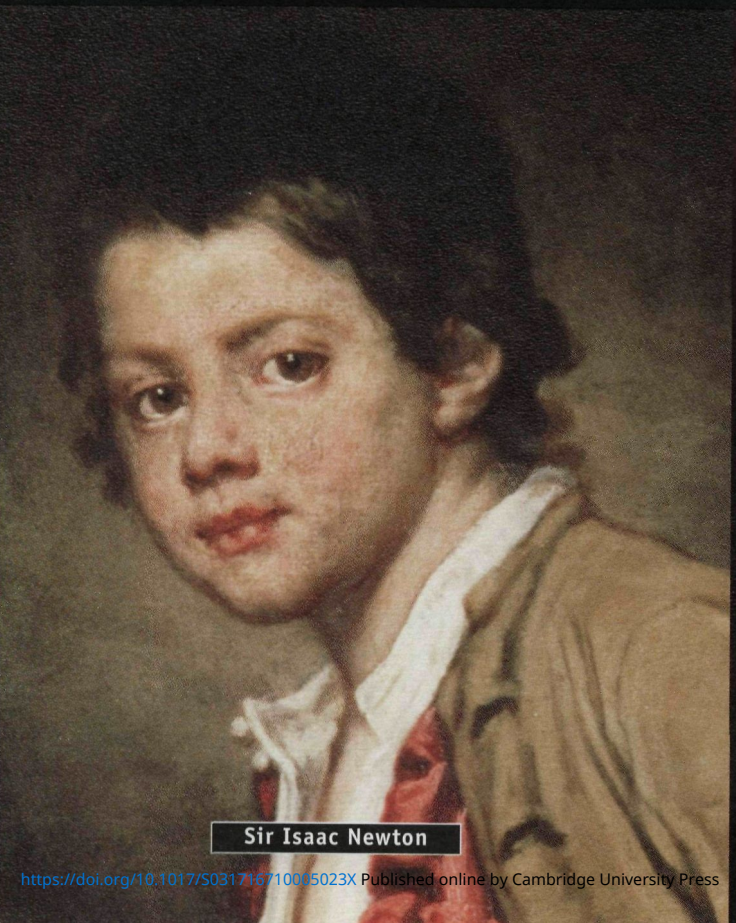
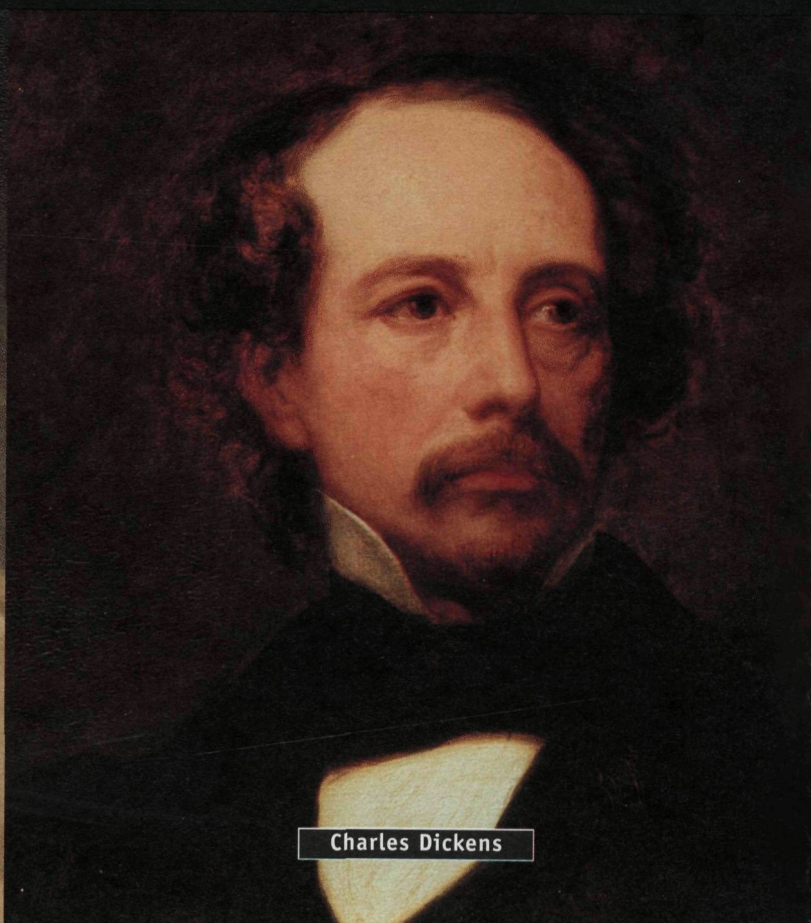


AUPARAVANT, LES PERSONNES ÉPILEPTIQUES DEVAIENT SE MONTRER EXCEPTIONNELLES POUR RÉUSSIR.





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EFFICACE CONTRE UN GRAND NOMBRE DE TYPES DE CRISES.

- TOPAMAX est efficace contre les crises partielles initiales, les crises tonico-cloniques primaires généralisées et les crises associées au syndrome de Lennox-Gastaut[1]
- Des résultats souhaitables avec absence totale de crises chez 19 % des adultes† et 22 % des enfants‡ atteints de crises partielles initiales[2,3]

AUCUN SIGNE D'EFFETS SECONDAIRES CAPABLES DE MENACER LE PRONOSTIC VITAL.

- Comme pour la plupart des antiépileptiques, les effets secondaires le plus fréquemment signalés relèvent du SNC et sont généralement légers à modérés et de nature passagère§[1]

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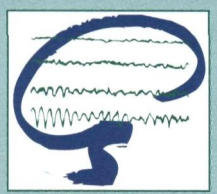
AUJOURD'HUI, IL Y A TOPAMAX.

UNE POSOLOGIE BIQUOTIDIENNE POUR TENIR COMPTE DU PATIENT.

- Le traitement par TOPAMAX peut être commencé et ajusté selon la réponse clinique quel que soit le traitement anticonvulsivant en cours
- Les comprimés sont inscrits au formulaire††

MAINTENANT OFFERT EN CAPSULES À SAUPOUDRER



TOPAMAX* topiramate

MAINTENANT INDIQUÉ CHEZ L'ENFANT

POUR AIDER LES PATIENTS À MIEUX PROFITER DE LA VIE

*Comprimés et capsules à saupoudrer *TOPAMAX* (topiramate) : indiqués comme traitement adjuvant chez les patients (adultes et enfants âgés de deux ans ou plus) atteints d'épilepsie dont l'état n'est pas maîtrisé de façon satisfaisante avec le traitement traditionnel. Les renseignements sur l'emploi du topiramate en monothérapie sont encore limités[1].*

†Une étude ouverte d'une durée de 20 semaines (n = 450 adultes). Posologie optimale : 300 à 350 mg/jour (moyenne : 288 mg/jour).
‡Étude ouverte portant sur des enfants (n = 72) traités pendant au moins 3 mois. Posologie moyenne : 10 mg/kg/jour.
§Manifestations indésirables liées au SNC : Somnolence (30,1 %), étourdissements (28,3 %), ataxie (21,2 %), troubles de la parole (16,8 %), ralentissement psychomoteur (16,8 %), nystagmus (15 %), paresthésie (15 %), nervosité (15,9 %), difficulté à se concentrer/troubles de l'attention (8 %), confusion (9,7 %), dépression (8 %), anorexie (5,3 %), problèmes de langage (6,2 %) et troubles de l'humeur (3,5 %). Une évaluation de 1 446 adultes et 303 enfants a indiqué que ces deux groupes semblent présenter des profils de manifestations indésirables similaires.
**Les effets à long terme d'une perte de poids chez les enfants ne sont pas connus.
††Médicament à usage limité : Ontario, Nouvelle-Écosse, Nouveau-Brunswick, Î.-P.-É. Remboursement intégral : Québec, Saskatchewan, Colombie-Britannique, Alberta, Manitoba.
Veuillez vous reporter aux Renseignements thérapeutiques sur TOPAMAX pour les détails thérapeutiques complets.

RÉFÉRENCES : **1.** Monographie des comprimés et capsules à saupoudrer TOPAMAX* (topiramate), 11 mai 1999. **2.** Kamin M, Kraut L, Olson W. Dose optimization of topiramate as add-on therapy in adults with treatment-resistant partial-onset seizures *Neurology* 1999;52 (Suppl 2):A525-526. **3.** Glauser TA, Elterman R, Wyllie E *et al.* Open label topiramate in paediatric partial epilepsy *Epilepsia* 1997:38 (Suppl. 3):94. **4.** Rosenfeld WE *et al.* Topiramate and concomitant weight loss. *Epilepsia* 1997:38 (Suppl 8):98.

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Nouveaux critères de la RAMQ†

Rebif®. Efficacité dépendante de la dose dans la SEP rémittente[1]*.

Pas encore

PrRebif®

Interféron bêta-1a

prêt à l'emploi

préremplie

Les effets secondaires les plus fréquemment observés sont les réactions au point d'injection et les symptômes pseudo-grippaux (asthénie, pyrexie, frissons, arthralgie, myalgie et céphalées). Leur fréquence et leur intensité tend à diminuer avec la poursuite du traitement. Veuillez consulter la monographie du produit pour les renseignements posologiques complets. Les données portant sur l'innocuité et l'efficacité proviennent d'observations sur 2 ans seulement.

* Rebif® est indiqué pour le traitement de la sclérose en plaques rémittente chez des patients dont la cote EDSS se situe entre 0 et 5,0, afin de réduire le nombre et la gravité des poussées cliniques, de ralentir la progression de l'invalidité physique, et de réduire les besoins de corticothérapie et le nombre de séjours à l'hôpital pour le traitement de la sclérose en plaques.

†Consultez votre représentant Serono pour plus de détails ou appelez au 1-877-777-3243.

RÉFÉRENCE :

[1] Groupe d'étude PRISMS (Prevention of Relapses and Disability by Interferon ß-1a Subcutaneously in Multiple Sclerosis), 1998. *Randomised double-blind placebo-controlled study of Interferon ß-1a in relapsing/remitting multiple sclerosis.* *Lancet*, 352:1498-1504

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