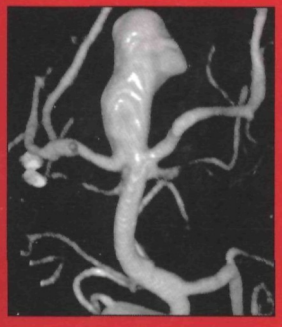
Volume 32 Number 1 February 2005

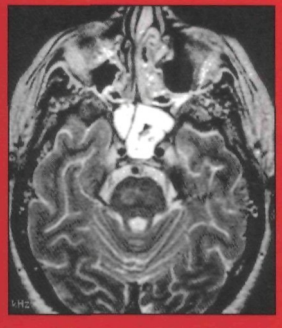
# THE CANADIAN JOURNAL OF Neurological Sciences

# LE JOURNAL CANADIEN DES Sciences Neurologiques

AN INTERNATIONAL JOURNAL / UN JOURNAL INTERNATIONAL



Aneurysm in the basilar apex



Neuropathological Conference



**40th CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES**
June 14-18, 2005
Ottawa, Ontario

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

# She Has Dreams. Controlling MS Could Help Her Live Them.

Jennifer M. is a MS patient who has been taking Rebif® since 1999. She lives in Vancouver.

**In PRISMS 4 – Patients treated early attained more benefit at 4 years than those delaying treatment.[1,2]***

- Rebif® 44mcg x3 reduced the number and severity of MS relapses.[1,2]*
- Time to sustained disability progression was prolonged by 18 months in the Rx44 group. (42.1 months vs. 24.2 months, p=0.047)[2]

Rebif® is indicated for the treatment of relapsing forms of multiple sclerosis, 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 and reduction in $T_1$-Gd enhanced and $T_2$ (burden of disease) as seen on MRI.[1] The most common adverse events reported in controlled clinical trials with high-dose Rebif® (44mcg x3) are: injection site inflammation 66.5%, injection site reaction 31.7%, injection site pain 13.8%, upper respiratory tract infections 20.4%, headache 46.7%, flu-like symptoms 42.5%, fatigue 27.5%, and fever 12.0%. Evidence of safety and efficacy derived from 3- and 4-year data.[1]

* Randomized, 4-year, placebo-controlled study. Patients receiving placebo in first 2 years were randomized to blinded interferon ß-1a, 22 or 44mcg x3 (n=172; crossover group) while others remained on assigned dose 22mcg (Rx22 group) or 44mcg (Rx44 group) *tiw* (n=167 per group). Patients had 3- to 6-month clinical and annual MRI assessments.

Rebif® is a registered trademark of Serono Canada Inc.

PAAB

Pr Rebif® 44mcg x3.
Interferon beta-1a
Because life is more than MS

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For brief prescribing information see pages A-18, A-19

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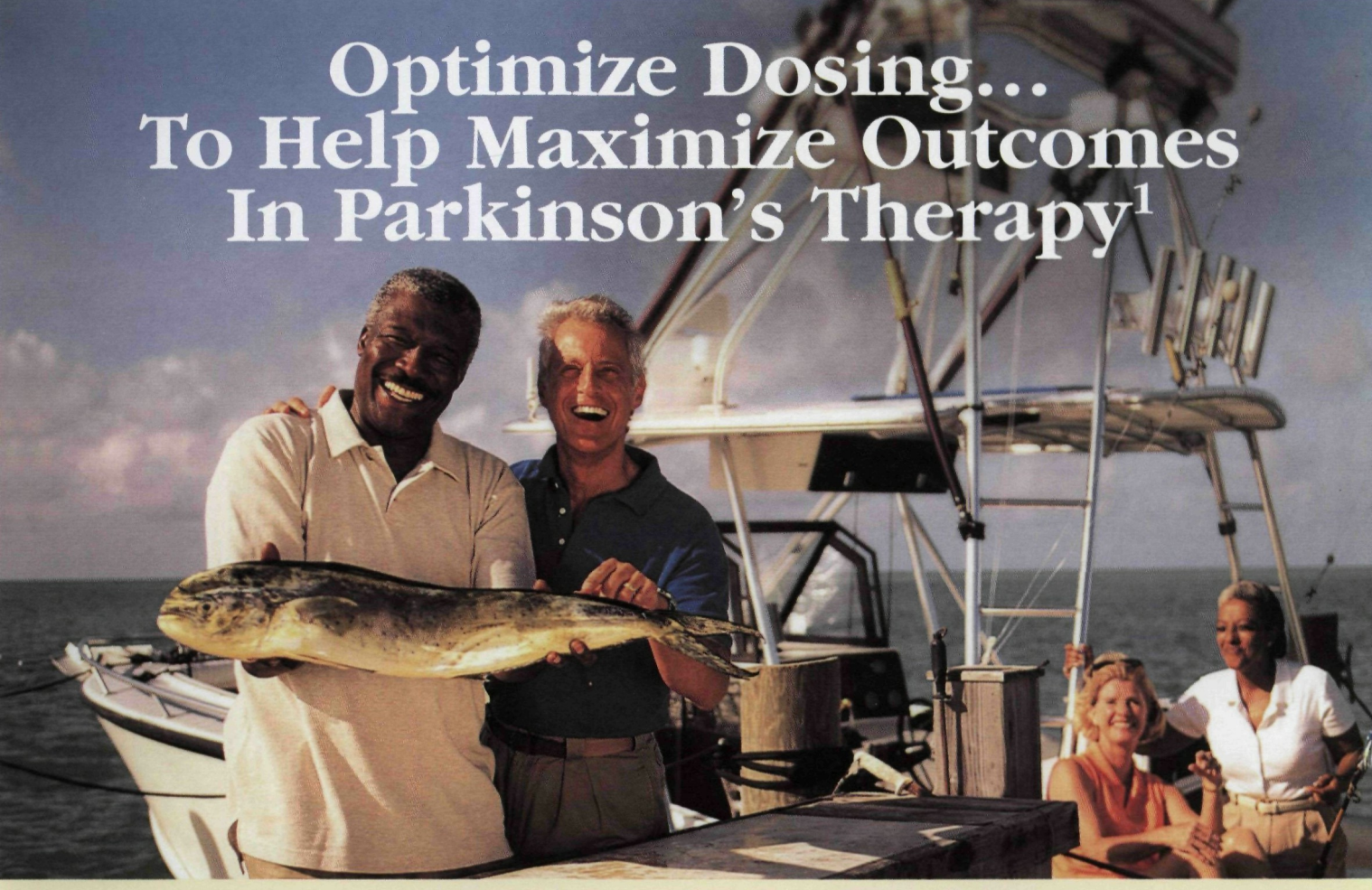
# Optimize Dosing... To Help Maximize Outcomes In Parkinson's Therapy[1]



*Titrate to help maximize patient benefit. In at least 75% of the patients who responded to REQUIP®, doses of up to 9 mg/day were necessary to ensure a first therapeutic response.*[1x]

## Three Reasons to Prescribe REQUIP®

### REQUIP® delayed the use of L-dopa

*34% (n=29 of 85) of REQUIP® monotherapy patients completed the entire 5-year study without requiring L-dopa supplementation*[2∂]

### Low risk of dyskinesia

*Only 5% of REQUIP® monotherapy patients developed dyskinesia compared with 36% of L-dopa patients*[2*]

### Low supplementary dose of L-dopa needed

*When used with adjunct L-dopa, REQUIP® patients required an average of 43% less L-dopa (427 ± 221 mg) than patients on L-dopa alone (753 ± 398 mg)*[2]

∂ In early treatment of Parkinson's disease over the course of a 5-year multicentre, prospective, double-blind, flexible-dose study, with 268 patients randomized to either REQUIP® (*n*=179) or L-dopa and benserazide (a decarboxylase inhibitor) (*n*=89). Open label L-dopa was available as supplementary medication.[2,3] $p<0.001$

* Prior to supplementation with L-dopa

*x* Data from 3 large phase III double-blind trials of ropinirole monotherapy in early Parkinson's disease were examined: a 5-year L-dopa-controlled trial (n=179), a 3-year bromocriptine-controlled trial (n=168), both with planned interim analysis and a 6-month placebo-controlled trial (n=116).[1]

† Please consult the Warnings section of the Product Monograph.[3]

® REQUIP is a registered trademark, used under license by GlaxoSmthKline Inc.

References: 1. Korczyn AD *et al.* Dosing with ropinirole in a clinical setting. *Acta Neurologica Scandinavica* 2002;106:200-204. 2. Rascol O *et al.* A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Eng J Med* 2000;342(20):1484-1491. 3. Product Monograph of REQUIP® (ropinirole hydrochloride), GlaxoSmithKline, March 2004.

REQUIP® (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease. REQUIP® can be used both as early therapy, without concomitant levodopa and as an adjunct to levodopa. Patients receiving treatment with REQUIP® and other dopaminergic agents have reported the sudden onset of sleep while engaged in daily activities. Patients should be warned not to drive or engage in other activities where impaired alertness could put themselves or others at risk.[3†]

Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: *Early therapy:* nausea, dizziness, somnolence, headache, peripheral edema, vomiting, syncope, fatigue and viral infection. *Adjunct therapy:* dyskinesia, nausea, dizziness, somnolence and headache. REQUIP® is contraindicated in patients with a known hypersensitivity to ropinirole hydrochloride or the excipients of the drug product.[3]

Pr REQUIP® ropinirole

**Rethinking Parkinson's.**

Member R&D PAAB

gsk GlaxoSmithKline

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# THE CANADIAN JOURNAL OF Neurological Sciences

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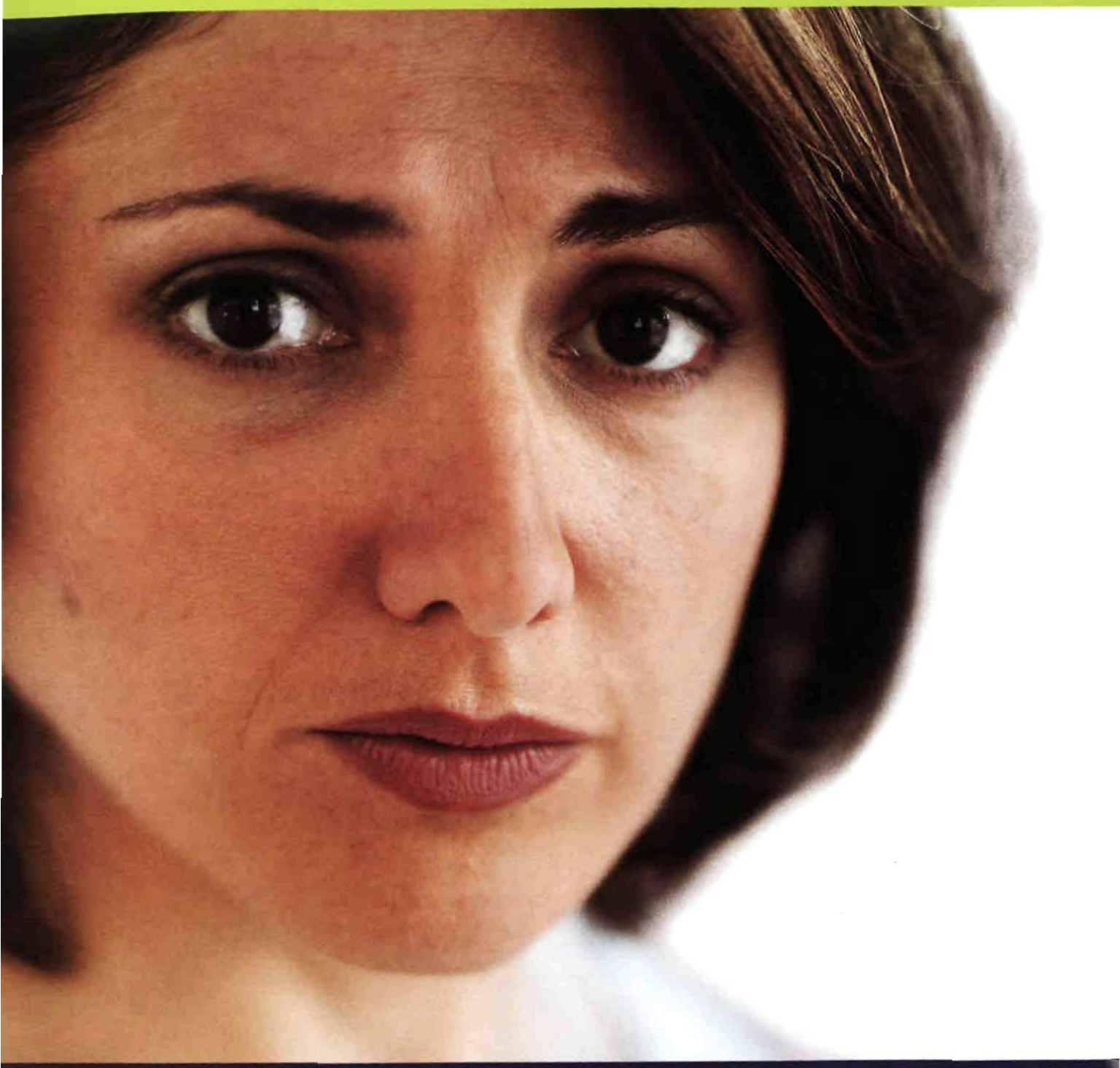

† 28-week, randomized, multicentre, double-blind, parallel-group, placebo-controlled U.S. study in patients (≥50 years) with moderate to severe Alzheimer's disease. Patients were randomized to treatment with EBIXA® 20 mg daily (n=126) or placebo (n=126).

* Function was measured on the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL$_{19}$) scale with LOCF data - Change from baseline at study endpoint for EBIXA® vs. placebo: 2.1 units, p = 0.02.

** Cognition was measured on the Severe Impairment Battery (SIB) with LOCF data - Change from baseline at study endpoint for EBIXA® vs. placebo: 5.9 units, p < 0.001.

Ω Less caregiver time was needed per month (45.8 hrs) for patients treated with EBIXA® vs. placebo, p=0.01.

1. Cummings JL. Alzheimer's disease (review). *New Engl J Med* 2004;351:56-67. 2. EBIXA® Product Monograph. Lundbeck Canada, Inc. 2004. 3. Reisberg B. *et al.* Memantine in Moderate-to-Severe Alzheimer's Disease. *N Engl J Med* 2003;348(14):1333-1341.



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# I've been living with Alzheimer's disease for three years.

My mother has the disease. But I feel just as helpless. Only someone who takes care of the patient truly knows how debilitating Alzheimer's disease is.[1] Introducing EBIXA®.

- A new class of therapy[2]
- Effective in moderate to severe stages[2]
- Extended daily functioning ($ADCS\text{-}ADL_{sev}$)[2,3†*] and cognition (SIB)[2,3†**] vs. placebo
- Generally well tolerated[2]
  Most common adverse events vs. placebo: dizziness (6.9% vs. 4.6%), constipation (6.1% vs. 3.5%), confusion (5.7% vs. 5.5%), and headache (5.6% vs. 3.6%).
- 45.8 hrs less caregiver time demonstrated per month vs. placebo[3Ω]

A new hope for patients with moderate to severe Alzheimer's disease.

EBIXA®, indicated for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type, 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 the clinical benefit. Patients should be advised of the nature of the authorization assessment.

NEW Ebixa®
memantine
A Name To Remember

EBIXA® (memantine hydrochloride) may be useful as monotherapy or as adjunctive therapy with cholinesterase inhibitors[3] for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type. EBIXA® has not been studied in controlled clinical trials for the symptomatic treatment of moderate to severe Alzheimer's disease for more than 6 months. There is no clinical evidence that EBIXA® alters the course of the underlying disease. Periodic monitoring of the patient's ophthalmic condition is recommended.

Caution should be observed when memantine is initiated in patients with cardiovascular conditions or in patients with a history of seizure disorder as these patient groups were not included in the clinical trials.

The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9, resulting in increased plasma levels of memantine.

Member R&D PAAB

Lundbeck

3 Cholinesterase inhibitors refers to only those which are approved in Canada for the symptomatic treatment of Alzheimer's disease.



For brief prescribing information see pages A-30, A-31, A-32

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Trust AVONEX

The **First and Only MS Therap**

indicated for use after a singl

demyelinating event



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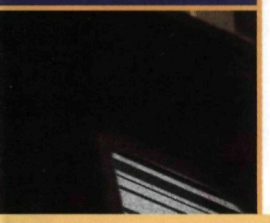

## ✓ Low Immunogenicity

- Neutralizing antibodies (NAbs) may significantly impact beta interferon's ability to bind to receptors and initiate an immunomodulatory process.

# INTERFERON WITH LESS INTERFERENCE

- AVONEX® (Interferon beta-1a) has demonstrated the lowest incidence of neutralizing antibodies (2-6%)*[1,2,3,4]

## ✓ Lasting Efficacy in MS Disease Activity**

- **44% reduction** in the risk of developing clinically definite MS in patients with a single demyelinating event over 3 years compared to placebo (confidence interval = 0.38 to 0.81; p=0.002)[Δ,5]
- **37% reduction** in the probability of disability progression at 2 years (21.9% vs. 34.9%; p=0.02)[+5]
- **32% reduction** in annual exacerbation rate over 2 years (0.61 vs. 0.90; p=0.002)[◊,5]

## ✓ Patient Convenience

- The only once-a-week MS therapy.

AVONEX® (Interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis to slow the progression of disability, decrease the frequency of clinical exacerbations, and reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans. AVONEX® is also indicated for the treatment of people who have experienced a single demyelinating event, accompanied by abnormal Magnetic Resonance Imaging (MRI) scans, with lesions typical of MS, to delay the onset of clinically definite multiple sclerosis (as determined by a second demyelinating event), and to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans). Before initiating treatment with AVONEX®, alternate diagnoses should first be excluded.

AVONEX® is generally well-tolerated. The most common side effects associated with treatment are flu-like symptoms, muscle ache, fever, chills, and asthenia. AVONEX® should be used with caution in patients with depression and in patients with seizure disorders. Patients with cardiac disease should be closely monitored. Routine periodic blood chemistry and hematologic tests are recommended during treatment with AVONEX®.

* Comparative clinical significance has not been established.
** As demonstrated in 3 years of clinical trials.
Δ Rate ratio = 0.56.
\+ Kaplan-Meier methodology. AVONEX® n=158, placebo n=143.
◊ AVONEX® n=85, placebo n=87.



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

EFFICACY THAT LASTS
As demonstrated in 3 years of clinical trials

biogen idec™

PAAB

2004-AVX-038

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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 on the website www.icmje.org, 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 (www.cjns.org). 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.

• ***Abstract*** Original Articles should be accompanied by an abstract of 250 words or less on a separate page, preferably in English and French, although the Journal will provide translation if required. Abstracts of original articles should consist of four paragraphs headed: *Background (or objective), Methods, Results and Conclusions.* Review articles should be accompanied by an abstract of 150 words or less.

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• The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. An ***Ethics approval statement*** must be provided, if applicable. 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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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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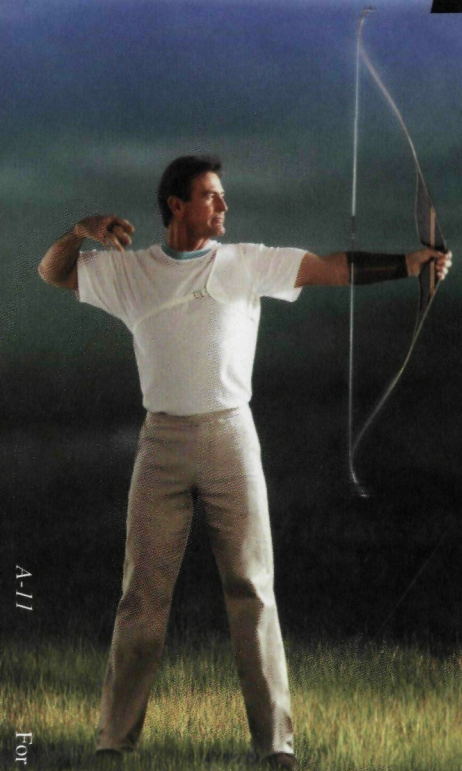
# PrLIPITOR*: Hitting targets.



NEW FLEXIBLE FIRST DOSE™

start at 10 mg, 20 mg, 40 mg††

†† When a >45% LDL-C reduction is required, patients may be started at 40 mg o.d.


Clinical research program[4]

*Aiming beyond.*

## LIPITOR has a leading edge clinical research program exploring new areas that may extend beyond lipid control[4]

**LIPITOR is an HMG-CoA reductase inhibitor (statin).** LIPITOR is indicated as an adjunct to lifestyle changes, including diet, for the reduction of elevated total cholesterol, LDL-C, TG and apolipoprotein B in hyperlipidemic and dyslipidemic conditions (including primary hypercholesterolemia, combined [mixed] hyperlipidemia, dysbetalipoproteinemia, hypertriglyceridemia and familial hypercholesterolemia) when response to diet and other non-pharmacological measures alone has been inadequate.

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and Total-C/HDL-C ratios (Fredrickson Type IIa and IIb).

Less than 2% of patients discontinued therapy due to adverse experiences. Most common adverse effects were constipation, diarrhea, dyspepsia, flatulence, nausea, headache, pain, myalgia and asthenia.

LIPITOR is contraindicated: During pregnancy and lactation; active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal; hypersensitivity to any component of this medication.

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

Caution should be exercised in severely hypercholesterolemic patients who are also renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently.

For brief prescribing information see pages A-28, A-29

**EFFICACY** ➢ † A powerful demonstrated effect across key lipid parameters[1]

**EXPERIENCE** ➢ More than **57** million patient-years of experience[2]

**EVIDENCE** ➢ Demonstrated delayed time to first ischemic event in stable CAD patients[3¥] (n=341, *p*=0.03)

¥ The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensive lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomized for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and a delayed time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is additive and complementary to angioplasty and would benefit patients referred for this procedure.[1]

PrLIPITOR atorvastatin calcium tablets

*power you can trust™*

10 mg 20 mg 40 mg 80 mg

Pfizer *Life is our life's work*



Kirkland, Quebec H9J 2M5

*TM Pfizer Ireland Pharmaceuticals Pfizer Canada Inc., licensee

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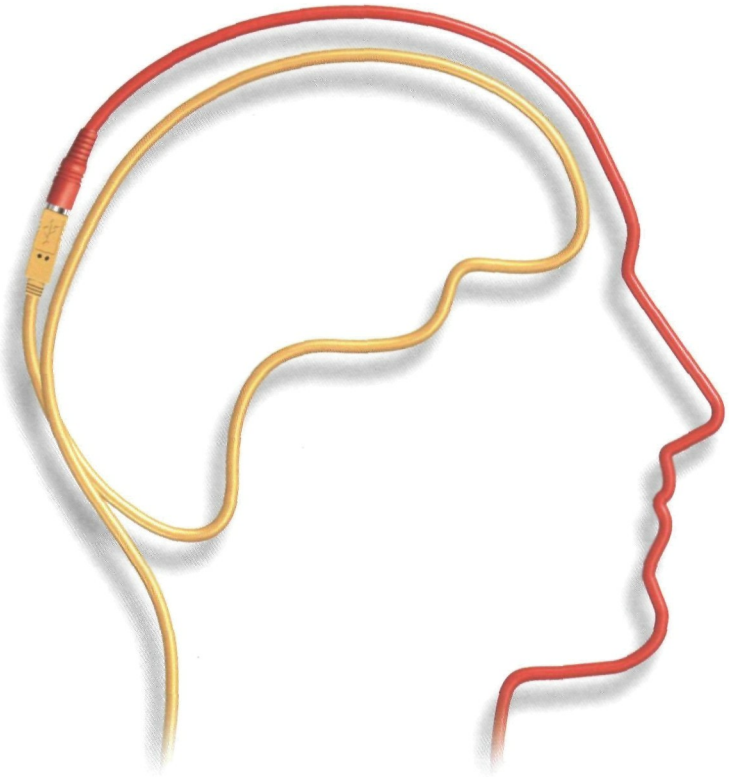

## Generally well tolerated

- Favourable adverse event profile
- Adverse events not dose dependent[2]
- Low discontinuation or dosage reduction (Keppra 14.3% vs placebo 11.7%) due to adverse events‡

## Efficacy and manageability right from the start

- Starting dose of 1000 mg/day (500 mg bid) shown to be effective and may be adjusted to a maximum of 3000 mg/day if required
- No blood level monitoring required
- No drug/drug interactions§ with other AEDs, warfarin, digoxin or between Keppra 500 mg bid and a combination oral contraceptive (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel)¶

¶ Note: Pharmacokinetic interaction studies with contraceptives have not been conducted covering the full recommended dosage range of Keppra. Physicians should advise their female patients to be alert to any irregular vaginal bleeding or spotting and report any occurrences.

* Restrictions may exist by province. Please refer to your formulary for details.

† Data from a 38-week multicentre, randomised, add-on, double-blind, placebo-controlled, parallel-group trial. Study consisted of a 4-week titration period followed by a 14-week evaluation period. Patients received either levetiracetam 1000 mg/day (n = 98), 3000 mg/day (n = 101) or placebo (n = 95). Patient weekly seizure frequency was reduced over placebo, at week 2 of the evaluation period, by 24.9% (1.120/1.406) for Keppra 1000 mg/day and 38.6% (0.918/1.406) for Keppra 3000 mg/day. The percentage of patients achieving ≥ 50% seizure reduction from baseline after the 18-week titration and evaluation period was 7.4% for placebo, 37.1% for Keppra 1000 mg/day and 39.6% for Keppra 3000 mg/day.

‡ Based on observations in clinical studies.

§ $C_{max}$ of levetiracetam's metabolite (ucb L057) was approximately doubled in presence of probenecid. Renal clearance of ucb L057 decreased by 60% in presence of probenecid.

Pr Keppra® levetiracetam

*CONNECTING EXCELLENT PROFILES IN EFFICACY AND TOLERABILITY*

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For brief prescribing information see pages A-22, A-23

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# PORTRAIT OF A FAMILY HISTORY

## HISTORY DOESN'T HAVE TO REPEAT ITSELF

Roger,
History of
angina.

Died age 57
of MI.

Alice,
History of
diabetes and
high total
cholesterol.

Died age 62
of stroke.

## Help Reduce the Risk of CV Death by 26%[1]

($p<0.001$; 6.1% vs. 8.1%)

**ALTACE® 10 mg**
ramipril

*GUARDING AGAINST CV DEATH*

ALTACE is indicated in the treatment of essential hypertension, normally when beta-blockers and diuretics are inappropriate. It may be used alone or in association with thiazide diuretics. ALTACE is indicated following acute myocardial infarction in clinically stable patients with signs of left ventricular dysfunction to improve survival and reduce hospitalizations for heart failure.

Results from the HOPE study showed that ALTACE improved survival in patients by reducing the risk of CV death by 26% ($p<0.001$; 6.1% vs. 8.1%). ALTACE may be used to reduce the risk of MI, stroke, or CV death in patients over age 55 who are at high risk of CV events because of a history of CAD, stroke, peripheral artery disease, or diabetes accompanied by at least 1 other CV risk factor such as hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria.

Like other ACE inhibitors, ALTACE is not recommended for pregnant or lactating women and should be used with caution in patients with renal insufficiency. The most frequent adverse events occurring in clinical trials with ALTACE monotherapy in hypertensive patients who were treated for at least 1 year ($n$=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%).

The reasons for stopping treatment were cough (ramipril 7.3% vs. placebo 1.8%); hypotension/dizziness (1.9% vs. 1.5%) and edema (0.4% vs. 0.2%).

## ALTACE is the most prescribed ACEI among cardiologists.*

*IMS Health Canada: Canadian CompuScript Audit, Moving Annual Total ending June 2004, Total Prescriptions.

Member R&D PAAB Product Monograph available to physicians and pharmacists upon request.

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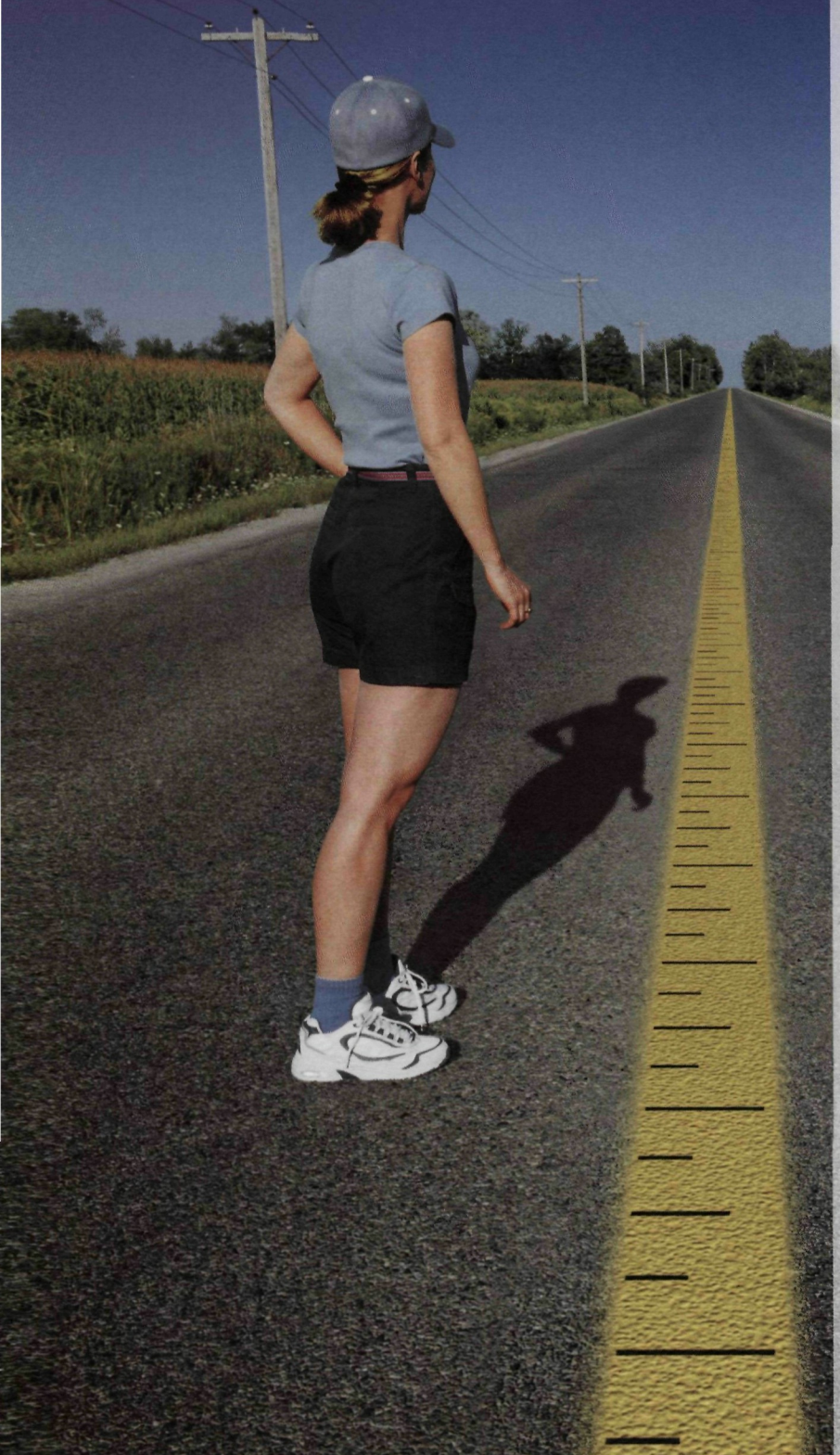
For brief prescribing information see pages A-17

Dans le traitement au long cours de la SP rémittente,

# vos patients peuvent compter sur COPAXONE®.



## Effet démontré sur l'incapacité

- Les patients traités par COPAXONE® ont présenté une réduction moyenne de leur cote EDSS de -0,05 comparativement à une augmentation de la cote EDSS de +0,21 dans le groupe placebo sur une période de deux ans.
  ({n = 125} c. {n = 126} placebo, $p = 0,023$)[1]

## Réduction de la fréquence des poussées*

- Réduction de 35 % après neuf mois
  (0,50 {n = 113} c. 0,77 {n = 115} placebo, moyenne, $p = 0,0077$)[1].
- Réduction de 75 % après deux ans
  (0,60 {n = 25} c. 2,40 {n = 25} placebo, moyenne, $p = 0,005$)[1].
  *Deux études indépendantes

## Profil d'innocuité établi

- Innocuité démontrée depuis plus de sept ans dans les essais cliniques[1].
- Aucune surveillance en laboratoire des anomalies hépatiques ou sanguines n'est recommandée[1].

L'emploi de COPAXONE® est indiqué chez les patients ambulatoires atteints de sclérose en plaques (SP) rémittente en vue de réduire la fréquence des poussées.

L'innocuité et l'efficacité de COPAXONE® dans la sclérose en plaques chronique progressive n'ont pas été établies.

Au cours des essais comparatifs, les effets indésirables le plus fréquemment associés à l'utilisation de COPAXONE® et dont l'incidence était supérieure à celle qui a été observée chez les sujets qui recevaient le placebo étaient les suivants : réactions au point d'injection (2,4-66,4 % c. 0-36,5 %), vasodilatation (27,2 % c. 11,1 %), douleur thoracique (26,4 % c. 10,3 %), asthénie (64,8 % c. 61,9 %), infection, douleur, nausées (23,2 % c. 17,5 %), arthralgie (24,8 % c. 17,5 %), anxiété et hypertonie (35,2 % c. 29,4 %).


# PrCOPAXONE®

(acétate de glatiramère injectable)

**Traitement au long cours de la SP rémittente**

TEVA NEUROSCIENCE



Pour documentation voir pages A-26, A-27

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