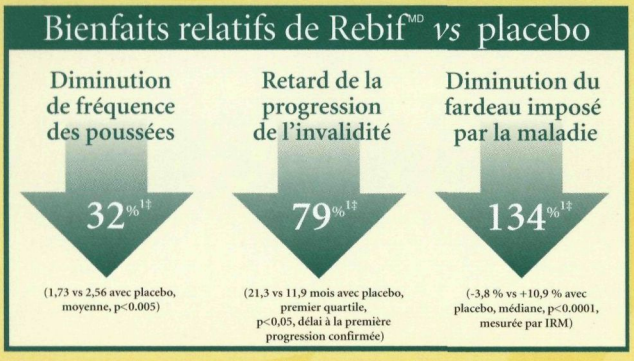
Volume 30 Number 4 November 2003

THE CANADIAN JOURNAL OF
Neurological Sciences
LE JOURNAL CANADIEN DES
Sciences Neurologiques

AN INTERNATIONAL JOURNAL / UN JOURNAL INTERNATIONAL

Subdural Electrodes

Visualisez ce que Rebif[MD] peut faire pour vos patients atteints de SEP[Δ].



Résultats de la dose de 44 mcg trois fois par semaine après 2 ans[1].

Au cours de deux études pivots incluant un total de 628 patients, Rebif a démontré une efficacité significative pour les trois paramètres principaux (poussées, progression de l'invalidité et IRM)[1,2].

Sa capacité de modifier le cours de la maladie[2] a fait non seulement de Rebif un bon médicament de première ligne pour la SEP rémittente, mais également le médicament dominant de sa catégorie[3].

Rebif est généralement bien toléré. Les effets indésirables les plus fréquents sont souvent traitables et diminuent en fréquence et en gravité avec le temps[2†].

Rebif modifie l'évolution naturelle de la SEP rémittente[2].

Rebif[MD] 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. Son efficacité a été confirmée au moyen d'évaluations IRM en T_1 marquées au Gd et d'évaluations IRM en T_2 (fardeau imposé par la maladie)[2].

† Les effets indésirables rapportés le plus souvent sont les suivants : réactions au point d'injection (toutes) (92,4 % *vs* 38,5 % pour le placebo), infections des voies respiratoires supérieures (74,5 % *vs* 85,6 % pour le placebo), céphalée (70,1 % *vs* 62,6 % pour le placebo), syndrome pseudo-grippal (58,7 % *vs* 51,3 % pour le placebo), fatigue (41,3 % *vs* 35,8 % pour le placebo) et fièvre (27,7 % *vs* 15,5 % pour le placebo). Les preuves d'innocuité et d'efficacité sont obtenues de l'étude de 2 ans seulement. Veuillez consulter la monographie du produit pour les renseignements d'ordonnance[2].

‡ Étude randomisée, à double insu, contrôlée par placebo. Groupe Rebif 44 mcg 3 fois/semaine (n = 184), groupe Rebif 22 mcg 3 fois/semaine (n = 189), groupe placebo (n = 187)[1].

Δ Le cas hypothétique peut ne pas représenter les résultats obtenus dans la population générale.

CCPP

Pr Rebif[MD]
interféron bêta-1ª

serono

POUR DE MULTIPLES RAISONS.

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Pour documentation voir pages A-26, A-27

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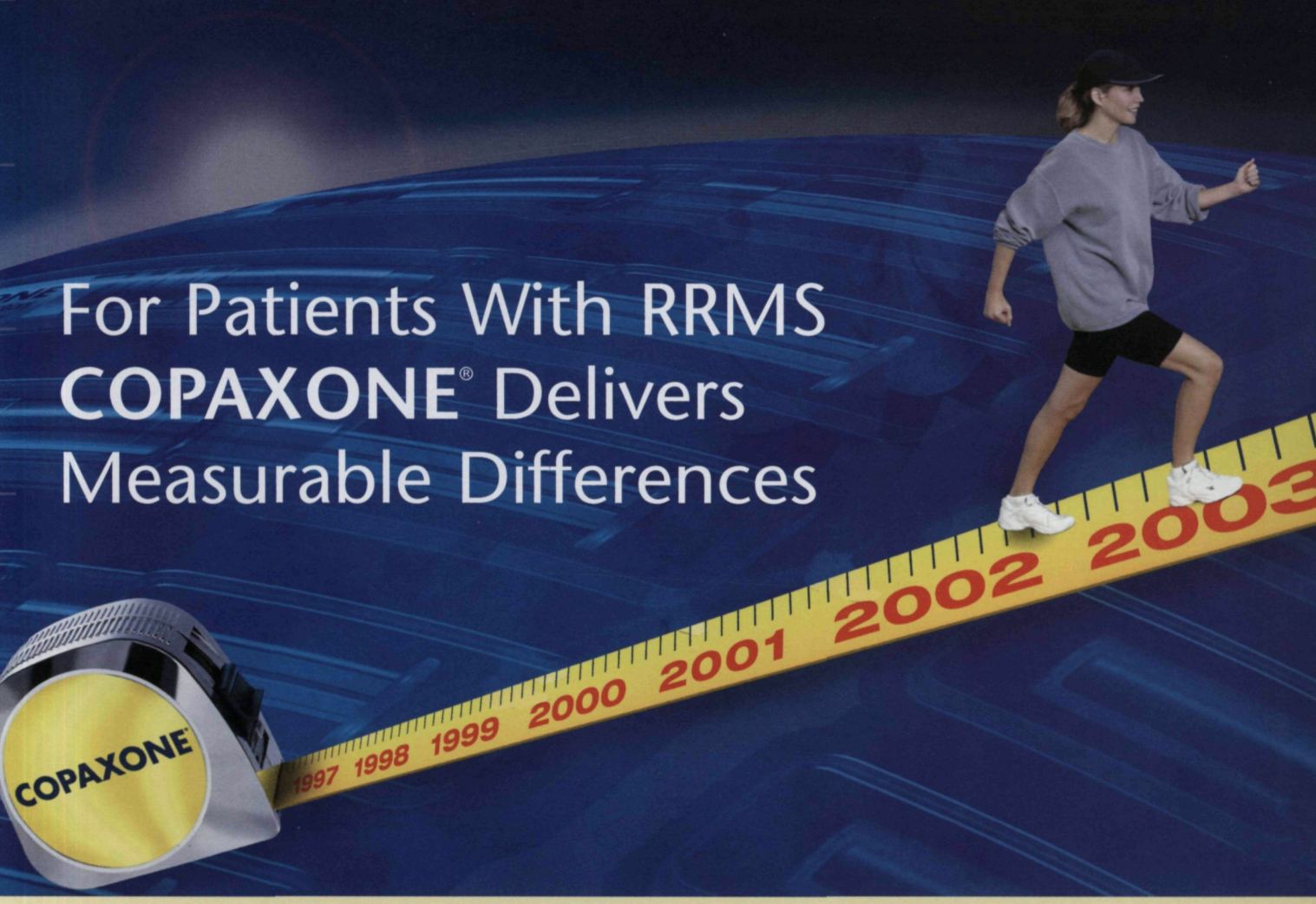

Demonstrated impact on disability

- COPAXONE®-treated patients experienced a significant improvement in mean EDSS change: 123% treatment effect vs. placebo over 2 years (-0.05 {n=125} vs. +0.21 {n=126}, p=0.023)[1]

Reduced relapse rates*

- 35% reduction at 9 months (0.50 {n=113} vs. 0.77 {n=115} placebo, mean, p=0.0077)[1]
- 75% reduction at 2 years (0.60 {n=25} vs. 2.40 {n=25} placebo, mean, p=0.005)[1]

*Two independent studies

Established safety profile

- Demonstrated for over 7 years in clinical trials[1]
- No recommended monitoring of liver and thyroid function or complete blood count[1]

COPAXONE® is indicated for use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis (RRMS) to reduce the frequency of relapses.
The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.
The most commonly observed adverse events associated with the use of COPAXONE® in controlled trials which occurred at higher frequency than placebo were: injection site reactions (2.4-66.4% vs. 0-36.5%), vasodilation (27.2% vs. 11.1%), chest pain (26.4% vs. 10.3%), asthenia (64.8% vs. 61.9%), infection, pain, nausea (23.2% vs. 17.5%), arthralgia (24.8% vs. 17.5%), anxiety and hypertonia (35.2% vs. 29.4%).

TEVA NEUROSCIENCE

PAAB

℗ COPAXONE®
(glatiramer acetate injection)

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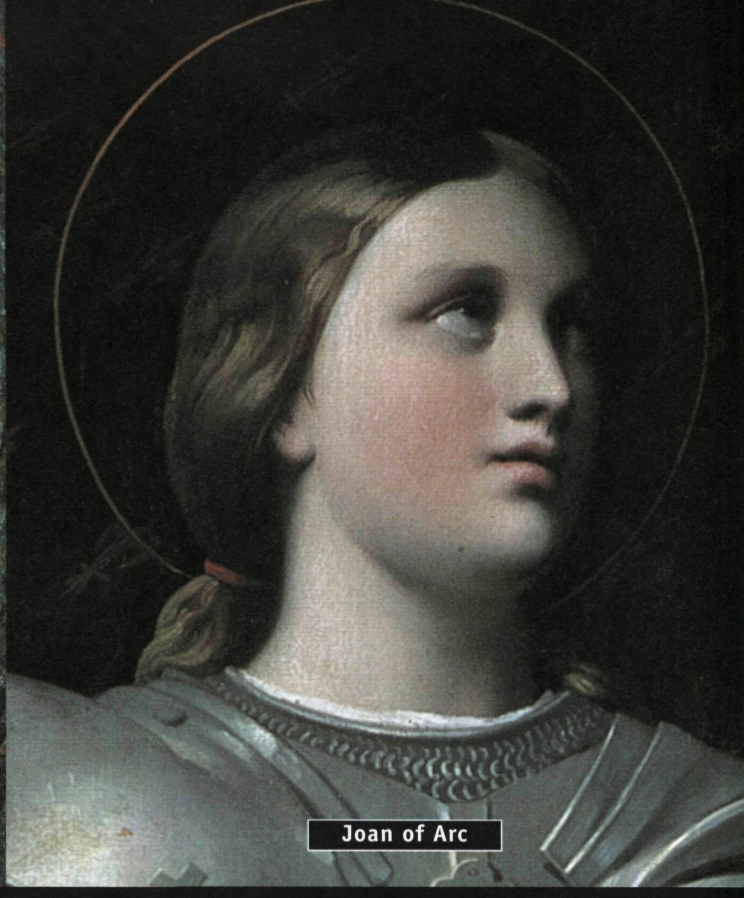
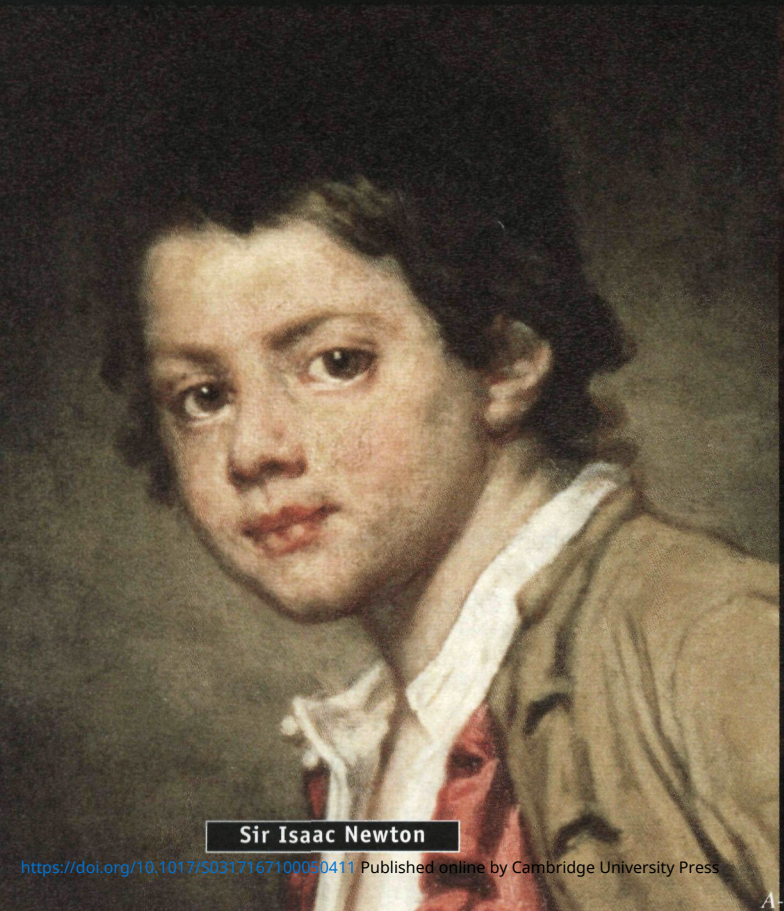
For brief prescribing information see pages A-30, A-31

Vincent Van Gogh

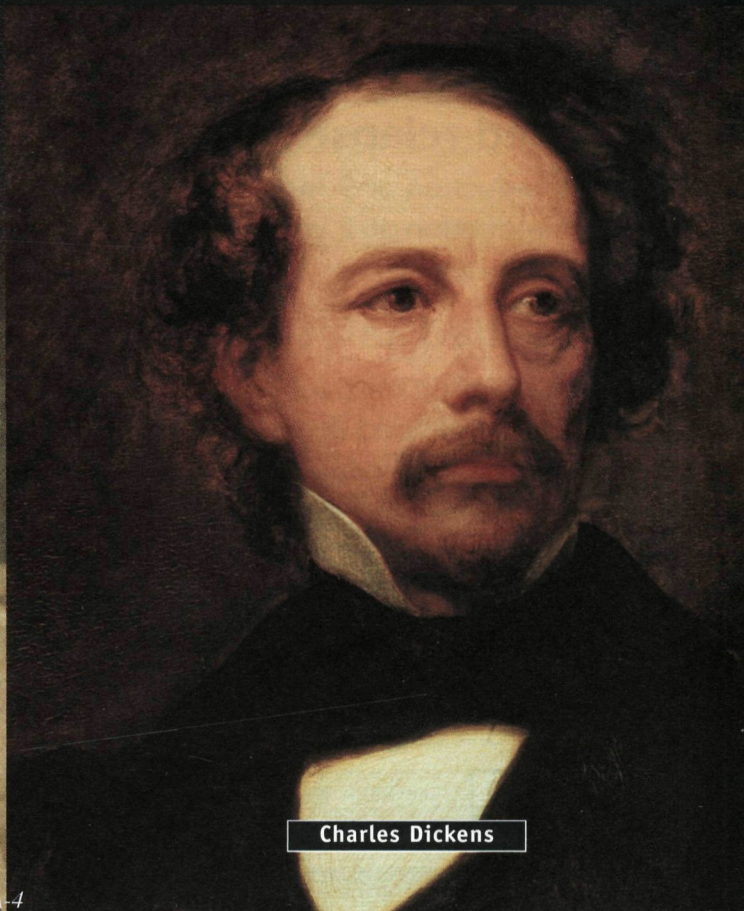


Joan of Arc

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



Sir Isaac Newton



Charles Dickens

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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.

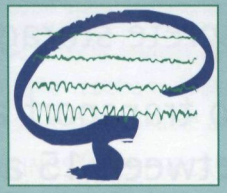
- 73% of patients (n = 52) showed a mean weight decrease of 5.97 lb (Interim analysis. Average duration 60 days)[4]
- 96% of children in clinical trials (≥ one year) who lost weight showed resumption of weight gain in test period**[1]

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.*[1]

† 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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NOW BET

"Now my family and I don't have to confront my MS every time I open the fridge door."

—Teresa, MS focus group, April 2002

REFRIGERATION-FREE
storage for a new level of convenience

- New discrete storage flexibility
- Easier to transport and travel with (keep between 15 and 30 °C)

Member R&D PAAB

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NEW REFRIGERATION-FREE STORAGE

TER THAN EVER

Same proven therapy

- Reduces relapse FREQUENCY and SEVERITY in RRMS[1-3]
- Backed by MS Pathways™ of Canada patient management support with toll-free hotline access to MS-specialized registered nurses

BETASERON® (interferon beta-1b) is indicated for the reduction of the frequency of clinical exacerbations in ambulatory patients with relapsing-remitting multiple sclerosis and for 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. Efficacy of treatment for longer than 2 years has not been substantially demonstrated in relapsing-remitting multiple sclerosis (RRMS).

The most common side effects related to BETASERON® in patients with RRMS are: flu-like syndrome (76%), fever (59%), chills (46%), injection-site reactions (85%), myalgia (44%), asthenia (49%) and malaise (15%).[2] Flu-like symptoms and injection-site reactions are manageable and lessen with time.[2]

FOR COMPLETE WARNINGS AND PRECAUTIONS, PLEASE REFER TO THE PRODUCT MONOGRAPH, AVAILABLE TO HEALTH CARE PROFESSIONALS UPON REQUEST.

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For brief prescribing information see pages A-34, A-35

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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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Our goal is to improve the quality of life of individuals suffering from psychiatric and neurological disorders.

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Interferon with Less Interference

For brief prescribing information see pages A-40

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

AVONEX® has demonstrated the lowest incidence of NAbs.[£,1,2,3,4]

- AVONEX treated patients had the lowest risk of becoming persistent NAb-positive; 2% of patients versus 15% and 31% for Rebif® (IFNß-1a 22 µg) and Betaseron® (IFNß-1b) respectively (Betaseron® vs AVONEX p=0.001, Betaseron® vs Rebif® p=0.19, Rebif® vs AVONEX p=0.04, n=125).[2]
- The majority of NAbs usually appear during the first 12 months after initiation of IFNß therapy (ranging from 3 to 18 months).[2,5]

Once-a-week AVONEX – Efficacy that Lasts

37% reduction in 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]

55% reduction in whole brain atrophy progression in year 2 (-0.233 vs. -0.521; p=0.03).[@,6]

89% reduction in Gd-enhanced lesions in patients with enhancement at baseline (0.11 vs 0.50; p=0.041).[†,7]

AVONEX is indicated for the treatment of relapsing forms of MS.[5] AVONEX is generally well tolerated.[5] The most common side effects associated with treatment are flu-like symptoms (muscle ache [myalgia], 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.

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

EFFICACY THAT LASTS
As demonstrated in 2 years of clinical trials

£ Comparative clinical significance has not been established.
¶ Kaplan-Meier methodology, AVONEX n=158, placebo n=143. * AVONEX n=85, placebo n=87.
@ As measured by brain parenchymal fraction, 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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PAAB

BIOGEN CANADA

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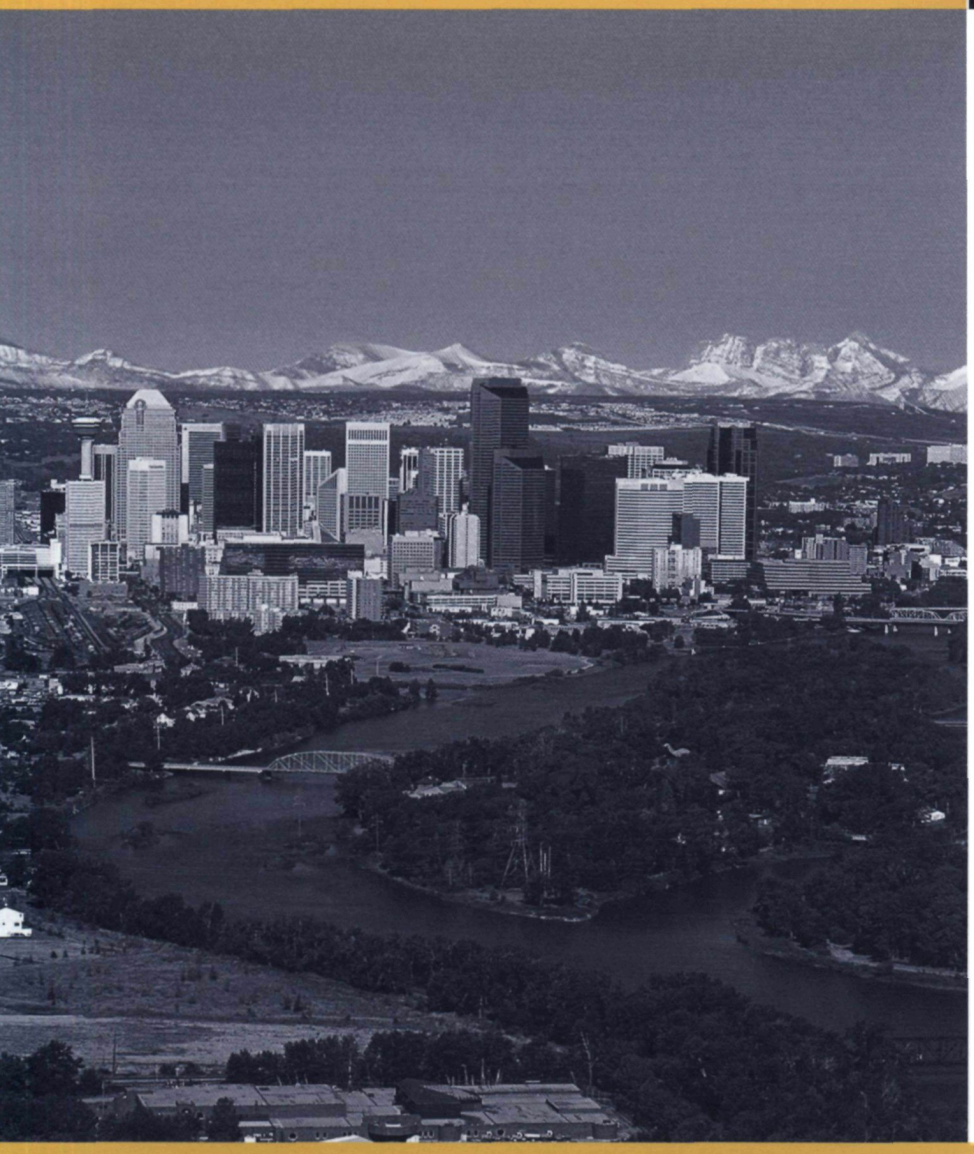

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meeting of the

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June 8-12 juin 2004

Tuesday June 8, 2004

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09:00-16:00 ALS-Strategies for Quality Life/Quality Care
18:00-21:00 Movement Disorders Video Session
18:00-21:00 Headache

Wednesday, June 9, 2004

08:00-17:30 Spinal Course
08:00-12:00 Brain Tumour Course
08:00-12:00 Epilepsy
08:00-12:00 EMG
13:30-17:30 Alzheimer's Disease
13:30-17:30 Gamma Knife
13:30-17:30 Movement Disorders
13:30-17:30 EEG
18:00-20:00 Welcome Reception

Thursday, June 10, 2004

08:30-10:30 Plenary Session I: Neurology and Neurosurgery in the Developing World
11:00-13:00 Platform Session
13:00-14:30 Poster Session
14:30-16:00 Platform Session
16:00-17:30 Grand Rounds
17:30-19:00 Poster Tours

Friday, June 11, 2004

08:30-10:30 Plenary Session II: New Directions in the Neurosciences
11:00-13:00 Platform Session
13:00-14:30 Poster Session
14:30-16:30 Plenary Session III: Risk Reduction in the Clinical Neurosciences
18:00 Social Night

Saturday, June 12, 2004

08:00-10:00 Neurocritical Care Mini-symposium
08:00-10:00 What's New in Neurology? Mini-symposium
08:00-10:00 How I do it … Neurosurgery. Mini-symposium
08:00-17:30 Child Neurology Day
10:30-17:00 Stroke
10:30-17:30 Multiple Sclerosis

PrALTACE® ramipril

PHARMACOLOGIC CLASSIFICATION:
Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY
ALTACE (ramipril) is an angiotensin converting enzyme (ACE) inhibitor.

Following oral administration, ALTACE is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

INDICATIONS AND CLINICAL USE: *Essential Hypertension.* ALTACE (ramipril) is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics. ALTACE should normally be used in patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. The safety and efficacy of ALTACE in renovascular hypertension have not been established and therefore, its use in this condition is not recommended. The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

Treatment Following Acute Myocardial Infarction
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. Sufficient experience in the treatment of patients with severe (NYHA class IV) heart failure immediately after myocardial infarction is not yet available. (See WARNINGS – Hypotension.)

MANAGEMENT OF PATIENTS AT INCREASED RISK OF CARDIOVASCULAR EVENTS: ALTACE may be used to reduce the risk of myocardial infarction, stroke or cardiovascular death in patients over 55 years of age who are at high risk of cardiovascular events because of a history of coronary artery disease, stroke, peripheral artery disease, or diabetes that is accompanied by at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, low high density lipoprotein levels, cigarette smoking, or documented microalbuminuria. The incidence of the primary outcome (composite of myocardial infarction, stroke and death from cardiovascular causes) was reduced from 17.8% in the placebo-treated group to 14.0% in the ramipril-treated group.

GENERAL: In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS). **When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy, and INFORMATION FOR THE PATIENT).**

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: *Angioedema:* Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered. *In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ALTACE (see ADVERSE REACTIONS – Treatment Following Acute Myocardial Infarction, DOSAGE AND ADMINISTRATION – Treatment Following Acute Myocardial Infarction).*

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease. Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: *As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of ALTACE should include appropriate assessment of renal function. ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.*

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Concomitant Diuretic Therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reducing initial dose. Agents increasing serum potassium: Use potassium sparing diuretics with caution and monitor frequently. Agents causing renin release: ALTACE antihypertensive effect increased. Lithium: Lithium levels may be increased. Administer lithium with caution and monitor levels frequently. Antacids: The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. Digoxin: No change in ramipril, ramiprilat or digoxin serum levels. Warfarin: The co-administration of ALTACE with warfarin did not alter the anticoagulant effects. Acenocoumarol: No significant changes. Non-steroidal anti-inflammatory agents (NSAID): The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (*e.g. indomethacin*).

ADVERSE REACTIONS: *Essential Hypertension.* Serious adverse events occurring in North American placebo-controlled clinical trials with ramipril monotherapy in hypertension (*n*=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ramipril patients (*n*=1,244), angioedema occurred in patients treated with ramipril and a diuretic (0.1%). The most frequent adverse events occurring in these trials with ALTACE monotherapy in hypertensive patients (*n*=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%). In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (*n*=972) have required discontinuation because of cough.

Treatment Following Acute Myocardial Infarction
Adverse events (except laboratory abnormalities) in a controlled clinical trial of post-AMI patients with clinical signs of heart failure considered possibly/probably related to ALTACE and occurring in more than 1% of stabilized patients (n=1,004) were: hypotension (10.7%); increased cough (7.6%); dizziness/vertigo (5.6%); nausea/vomiting (3.8%); angina pectoris (2.9%); postural hypotension (2.2%); syncope (2.1%); heart failure (2.0); severe/resistant heart failure (2.0%); myocardial infarction (1.7%); vomiting (1.6%); headache (1.2%); abnormal kidney function (1.2%); abnormal chest pain (1.1%); diarrhea (1.1%). Isolated cases of death have been reported with the use of ramipril that appear to be related to hypotension (including first dose effects), but many of these are difficult to differentiate from progression of underlying disease (see WARNINGS – Hypotension). Discontinuation of therapy due to adverse reactions was required in 368/1,004 post-AMI patients taking ramipril (36.7%), compared to 401/982 patients receiving placebo (40.8%).

Clinical Laboratory Test Findings: increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

DOSAGE AND ADMINISTRATION

Essential Hypertension: Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg of ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/1.73 m² (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg of ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73 m²) the maximum total daily dose of 2.5 mg of ALTACE should not be exceeded.

Treatment Following Acute Myocardial Infarction:
Initiation of therapy requires consideration of concomitant medication and baseline blood pressure and should be instituted under close medical supervision, usually in a hospital, three to ten days following an acute myocardial infarction in haemodynamically stable patients with clinical signs of heart failure. The recommended initial dosage of ALTACE is 2.5 mg given twice a day (b.i.d.), one in the morning and one in the evening. If tolerated, and depending on the patient's response, dosage may be increased by doubling at intervals of one to three days. The maximum daily dose of ALTACE should not exceed 5 mg twice daily (b.i.d). After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If a patient becomes hypotensive at this dosage, it is recommended that the dosage be lowered to 1.25 mg b.i.d. following effective management of the hypotension. (see WARNINGS – Hypotension).

Patients who have been fluid or salt depleted, or treated with diuretics are at an increased risk of hypotension (see WARNINGS – Hypotension). An excessive fall in blood pressure may occur particularly in the following: after the initial dose of ALTACE; after every first increase of dose of ALTACE; after the first dose of a concomitant diuretic and/or when increasing the dose of the concomitant diuretic. If appropriate, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension (see PRECAUTIONS – Drug Interactions). Consideration should be given to reducing the initial dose to 1.25 mg of ALTACE in these patients.

Use in Renal Impairment: In patients with impaired renal function (creatinine clearance of 20-50 mL/min/1.73 m² body surface area), the initial recommended dosage is generally 1.25 mg of ALTACE once daily. This dosage may be increased with caution up to 1.25 mg of ALTACE twice daily, depending upon clinical response and tolerability.

Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and severe renal failure. (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Renal Impairment).

Use in Hepatic Impairment: Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and hepatic dysfunction. Dose reduction and careful monitoring of these patients is required (see ACTIONS AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Patients with Impaired Liver Function).

Management of Patients at Increased Risk of Cardiovascular Events: Recommended initial dose: 2.5 mg of ALTACE once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and – after another three weeks – to increase it to 10 mg. Usual maintenance dose: 10 mg of ALTACE daily (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS). Dosage recommendations for special risk groups such as patients with renal or hepatic impairment, or at an increased risk of hypotension (fluid or salt depletion, treated with diuretics) are to be followed as previously described (see WARNINGS and PRECAUTIONS).

DOSAGE FORM

a) Composition
ALTACE (ramipril) capsules 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg contain the medicinal ingredient ramipril in quantities of 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg respectively. The qualitative formulation for all potencies of ALTACE is: ramipril, pre-gelatinized starch NF (as filler, gliding agent and disintegration agent) and empty gelatin capsules. Empty gelatin capsules for all potencies of ALTACE are composed of gelatin NF and coloring agents specific to each potency (see below).

POTENCY	CAP	BODY
1.25 mg	Yellow iron oxide Titanium dioxide	Titanium dioxide
2.5 mg	Yellow iron oxide FD & C red no. 3 Titanium dioxide	Titanium dioxide
5.0 mg	FD & C blue no. 2 FD & C red no. 3 Titanium dioxide	Titanium dioxide
10.0 mg	FD & C blue no. 2 FD & C red no. 3 Black iron oxide Titanium dioxide	Titanium dioxide

b) Stability and storage recommendations
Store ALTACE (ramipril) in original container at room temperature, below 25°C and not beyond the date indicated on the container.

AVAILABILITY: No. 4 hard gelatin capsules:
- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5.0 mg (white/red);
- 10.0 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules. Bottles of 100 capsules and 500 capsules also available.

Product monograph available upon request.

References:
1. ALTACE Product Monograph. 2. The Heart Outcomes Prevention Evaluation Study Investigators (HOPE) Trial. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342(3):145-53.

See page A-17

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For brief prescribing information see page A-16

BETA

« *Maintenant, ma famille et moi ne faisons plus face à ma SEP chaque fois que nous ouvrons la porte du réfrigérateur.* »

—Teresa, groupe de discussion sur la SEP, avril 2002

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Membre R&D CCPP

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NOUVELLE PRÉPARATION
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SERON...
À SON MEILLEUR !

Le même traitement éprouvé

- Réduction de la FRÉQUENCE et de la GRAVITÉ des poussées en SEP rémittente[1-3]
- Soutien téléphonique sur la prise en charge fourni sans frais par SEP-ACCÈS[MD] pour le Canada et permettant au patient d'être en communication directe avec une infirmière spécialisée en SEP

BETASERON® (interféron bêta-1b) est indiqué pour réduire la fréquence des poussées cliniques chez les patients ambulatoires atteints de sclérose en plaques rémittente. Il est également indiqué pour ralentir la progression de l'incapacité et réduire la fréquence des poussées cliniques chez les patients atteints de sclérose en plaques progressive-secondaire.

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.

Chez les patients atteints de SEP rémittente, les effets indésirables les plus courants liés à l'utilisation de BETASERON® sont : syndrome pseudo-grippal (76 %), fièvre (59 %), frissons (46 %), réactions au point d'injection (85 %), myalgie (44 %), asthénie (49 %) et malaise (15 %)[2]. Les symptômes pseudo-grippaux et les réactions au point d'injection peuvent être traités et diminuent avec le temps[2].

POUR PLUS DE DÉTAILS SUR LES MISES EN GARDE ET LES PRÉCAUTIONS, VEUILLEZ CONSULTER LA MONOGRAPHIE DE PRODUIT FOURNIE SUR DEMANDE AUX PROFESSIONNELS DE LA SANTÉ.

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Pour documentation voir pages A-34, A-35

Pr ropinirole® REQUIP®

Ropinirole (as ropinirole hydrochloride)

TABLETS: 0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION: AntiParkinsonian Agent / Dopamine Agonist

INDICATIONS AND CLINICAL USE: 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. Three year and five year active-comparator controlled clinical trials have been conducted.

CONTRAINDICATIONS: REQUIP® (ropinirole hydrochloride) is contraindicated in patients with a known hypersensitivity to ropinirole hydrochloride or the excipients of the drug product.

WARNINGS: Sudden Onset of Sleep – Patients receiving treatment with REQUIP® (ropinirole hydrochloride), and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on REQUIP®, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician. Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products. Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness. There is insufficient information to determine whether this event is associated with REQUIP®, all dopaminergic agents or Parkinson's disease itself. **Orthostatic Symptoms** – Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting orthostatic symptoms of dizziness or lightheadedness, with or without documented hypotension. These symptoms appear to occur especially during dose escalation. Therefore, patients treated with dopamine agonists should be carefully monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation (see DOSAGE and ADMINISTRATION) and should be informed of this risk. **Hallucinations** – ***Early Therapy***: In placebo- controlled trials, REQUIP® (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group). Hallucination was of sufficient severity that it led to discontinuation in 1.3% of patients. The incidence of hallucination was dose-dependent. In a 5-year study comparing REQUIP® with levodopa in early Parkinson's patients, the overall incidence of hallucinations was 17.3% (31/179) for patients treated with REQUIP® and 5.6% (5/89) for levodopa patients. Hallucinations led to discontinuation of the study treatment in 5.0% of REQUIP® and 2.2% of levodopa patients. In a 3-year study comparing REQUIP® with another dopamine agonist, the overall incidence of hallucinations was 9.5% (16/168) for patients treated with REQUIP® and 9.0% (15/167) for patients receiving active comparator. Hallucinations led to discontinuation of the study treatment in 2.4% of REQUIP® patients and 3.0% of comparator patients. Concomitant Selegiline: In a 5-year study, REQUIP® patients receiving concomitant selegiline reported a higher incidence of hallucinations (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa arm (hallucinations with concomitant selegiline = 2.0% vs hallucinations without selegiline = 8.0%). ***Adjunct Therapy***: Hallucinations were experienced by 10.1% of patients receiving REQUIP® and levodopa, compared to 4.2% receiving placebo and levodopa. Hallucinations were of sufficient severity that it led to discontinuation in 1.9% of patients. The incidence of hallucinations was dose dependent.

PRECAUTIONS: Cardiovascular – Since REQUIP® (ropinirole hydrochloride) has not been studied in patients with a history or evidence of significant cardiovascular disease including myocardial infarction, unstable angina, cardiac decompensation, cardiac arrhythmias, vaso-occlusive disease (including cerebral) or cardiomyopathy, it should be used with caution in such patients. There is limited experience with REQUIP® in patients treated with antihypertensive and antiarrhythmic agents. Consequently, in such patients, the dose of REQUIP® should be titrated with caution. **Orthostatic Symptoms** - Orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP® therapy. **Neuroleptic Malignant Syndrome** – A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. A single spontaneous report of a symptom complex resembling the neuroleptic malignant syndrome has been observed in a 66 year old diabetic male patient with Parkinson's disease, who developed fever, muscle stiffness, and drowsiness 8 days after beginning REQUIP® treatment. The patient also experienced acute bronchitis, which did not respond to antibiotic treatment. REQUIP® was discontinued three days before the patient died. The reporting physician considered these events to be possibly related to REQUIP® treatment. (see DOSAGE AND ADMINISTRATION). A single spontaneous report of severe muscle pain has been reported in a 66 year old male patient around his thigh. The reporting physician considered the event to be probably related to REQUIP® treatment. **Retinal Pathology in Rats** – In a two year carcinogenicity study in albino Sprague-Dawley rats, retinal atrophy was observed at incidences of 0%, 1.4%, 1.4% and 10% of male rats and 0%, 4.4%, 2.9% and 12.9% of female rats dosed at 0, 1.5, 15 and 50 mg/kg/day respectively. The incidence was significantly higher in both male and female animals dosed at 50 mg/kg/day. The 50 mg/kg/day dose represents a 2.8 fold greater exposure (AUC) and a 13.1 fold greater exposure (C_{max}) to ropinirole in rats than the exposure would be in humans at the maximum recommended dose of 24 mg/day. The relevance of this finding to humans is not known. **Pregnancy** – The use of REQUIP® during pregnancy is not recommended. REQUIP® given to pregnant rats during organogenesis (gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day (approximately 3–4 times the AUC at the maximal human dose of 8 mg t.i.d.), increased fetal death at 90 mg/kg/day (approximately 5 times the AUC at the maximal human dose of 8 mg t.i.d.) and digital malformations at 150 mg/kg/day (approximately 8–9 times the AUC at the maximal human dose of 8 mg t.i.d.). These effects occurred at maternally toxic doses. There was no indication of an effect on development of the conceptus at a maternally toxic dose of 20 mg/kg/day in the rabbit. In a perinatal-postnatal study in rats, 10 mg/kg/day of REQUIP® (approximately 0.5 – 0.6 times the AUC at the maximal human dose of 8 mg t.i.d.) impaired growth and development of nursing offspring and altered neurological development of female offspring. **Nursing Mothers** – Since REQUIP® suppresses lactation, it should not be administered to mothers who wish to breast-feed infants. Studies in rats have shown that REQUIP® and/or its metabolites cross the placenta and are excreted in breast milk. Consequently, the human fetus and/or neonate may be exposed to dopamine agonist activity. **Use in Women Receiving Estrogen Replacement Therapy**– In female patients on long-term treatment with conjugated estrogens, oral clearance was reduced and elimination half-life prolonged compared to patients not receiving estrogens. In patients, already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **Pediatric Use** – Safety and effectiveness in the pediatric population have not been established. **Renal and Hepatic Impairment** – No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min). Because the use of REQUIP® in patients with severe renal impairment or hepatic impairment has not been studied, administration of REQUIP® to such patients is not recommended. **Drug Interactions** – ***Psychotropic Drugs:*** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of REQUIP®. Therefore, concomitant use of these products is not recommended. Based on population pharmacokinetic assessment, no interaction was seen between REQUIP® and tricyclic antidepressants or benzodiazepines. ***Anti-Parkinson Drugs:*** Based on population pharmacokinetic assessment, there were no interactions between REQUIP® and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics. ***Levodopa:*** The potential pharmacokinetic interaction of levodopa/ carbidopa (100 mg/10 mg b.i.d.) and REQUIP® (2 mg t.i.d.) was assessed in levodopa naive (de novo) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of REQUIP® at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP®. ***Inhibitors of CYP1A2: Ciprofloxacin:*** The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 55 years). The extent of systemic availability of REQUIP® was significantly increased when coadministered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, REQUIP® therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage will be required. ***Substrates of CYP1A2: Theophylline:*** The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 59 years). There was no marked change in the rate or extent of availability of REQUIP® when coadministered with theophylline. Similarly, coadministration of REQUIP® with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of REQUIP®, and vice-versa. ***Digoxin:*** The effect of REQUIP® (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125–0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10, mean age 72 years). Coadministration at steady state with REQUIP® resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of REQUIP® on the pharmacokinetics of digoxin is not known. ***Alcohol:*** No information is available on the potential for interaction between REQUIP® and alcohol. As with other centrally active medications, patients should be cautioned against taking REQUIP® with alcohol. **Psycho-Motor Performance** – (see WARNINGS - Sudden Onset of Sleep).

ADVERSE REACTIONS: Adverse Reactions Associated with Discontinuation of Treatment – Of 1599 patients who received REQUIP® (ropinirole hydrochloride) during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of REQUIP® in 1% or more of patients were as follows: ***Early therapy:*** nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). ***Adjunct therapy:*** dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age. **Most Frequent Adverse Events** – 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. Dopamine agonists, with an ergoline chemical structure have been associated with adverse experiences such as retroperitoneal fibrosis, erythromelalgia and pulmonary reactions. REQUIP® has a novel, non-ergoline chemical structure and no reports of such events have been observed in clinical trials. **Incidence of Adverse Events in Placebo Controlled Trials** – The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to < 90 mmHg have been observed in 13% (<65 years), 16% (65 – 75 years) and 7.6% (>75 years) of patients treated with REQUIP®. **Table 2** lists adverse events that occurred at an incidence of 1% or more among REQUIP®-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization (WHO)-based dictionary terminology. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies can not be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence rate in the population studied.

TABLE 2
Adverse events with incidence ≥1% from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 206 % occurrence	Placebo N = 120 % occurrence
Autonomic Nervous System				
Sweating Increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	–	–
Injury	–	–	10.6	9.2
Pain	7.6	4.1	5.3	3.3
Asthenia	6.4	1.4	–	–
Drug Level Increased	4.5	2.7	6.7	3.3
Chest Pain	3.8	2.0	–	–
Malaise	3.2	0.7	1.4	0.8
Therapeutic Response Decreased	1.9	0.7	–	–
Cellulitis	1.3	0.0	–	–
Influenza-like Symptoms	–	–	1.0	0.0
Fever	–	–	1.4	0.0
Cardiovascular General				
Syncope	11.5	1.4	2.9	1.7
Hypotension Postural	6.4	4.8	–	–
Hypertension	4.5	3.4	3.4	3.3
Hypotension	1.9	0.0	2.4	0.8
Cardiac Failure	–	–	1.0	0.0
Central and Peripheral Nervous System				
Dizziness	40.1	21.8	26.0	15.8
Dyskinesia	–	–	33.7	12.5
Headache	17.2	17.0	16.8	11.7
Ataxia (Falls)	–	–	9.6	6.7
Tremor	–	–	6.3	2.5
Paresthesia	–	–	5.3	2.5
Hyperesthesia	3.8	2.0	–	–
Dystonia	–	–	4.3	4.2
Hypokinesia	–	–	5.3	4.2
Paresis	–	–	2.9	0.0
Speech Disorder	–	–	1.0	0.0
Vertigo	1.9	0.0	–	–
Carpal Tunnel Syndrome	1.3	0.7	–	–
Gastrointestinal System				
Nausea	59.9	21.8	29.8	18.3
Vomiting	12.1	6.8	7.2	4.2
Dyspepsia	9.6	4.8	–	–
Constipation	8.3	7.5	5.8	3.3
Abdominal Pain	6.4	2.7	8.7	7.5
Diarrhea	–	–	4.8	2.5
Anorexia	3.8	1.4	–	–
Flatulence	2.5	1.4	1.9	0.8
Tooth Disorder	1.9	0.7	1.0	0.8
Saliva Increased	–	–	2.4	0.8
Colitis	1.3	0.0	-	-
Dysphagia	1.3	0.0	2.4	0.8
Periodontitis	1.3	0.0	1.4	0.8
Eructation	–	–	1.4	0.0
Fecal Incontinence	–	–	1.0	0.0
Hemorrhoids	–	–	1.0	0.0
Gastroesophageal Reflux	–	–	1.0	0.0
Gastrointestinal Disorder (NOS)	–	–	1.0	0.0
Tooth Ache	–	–	1.0	0.0
Hearing and Vestibular				
Tinnitus	1.3	0.0	–	–
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5

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Continued on page A-41

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.[1Ω] Yet ReQuip® 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.

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. Three year and five year active-comparator controlled clinical trials have been conducted.

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.[†††]

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.

† Hoehn and Yahr stages I-II.

Ω A 6-month interim analysis of a 5-year, double-blinded, randomized, multicentre 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 patients receiving ropinirole was 1.2% and in patients receiving L-dopa was 11.2%. Meta analysis, *n*=515, 17 months.

††† Please consult the Warnings section of the Prescribing Information.

Pr REQUIP® ropinirole

Rethinking Parkinson's.

gsk GlaxoSmithKline

PAAB Member R&D

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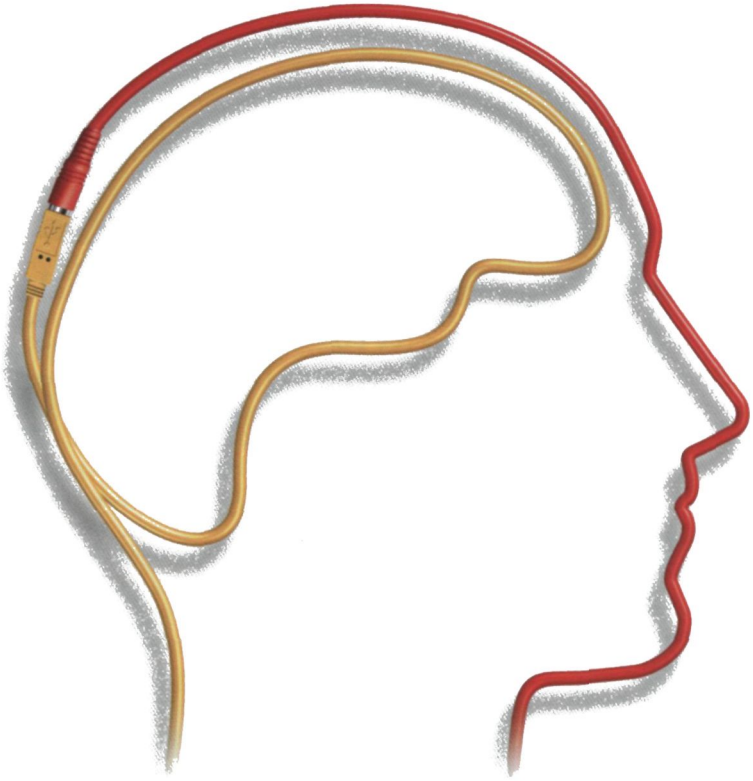
to control



Generally well tolerated

- Favourable side effect 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.

* 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.

NEW Pr Keppra® levetiracetam

CONNECTING EXCELLENT PROFILES IN EFFICACY AND TOLERABILITY

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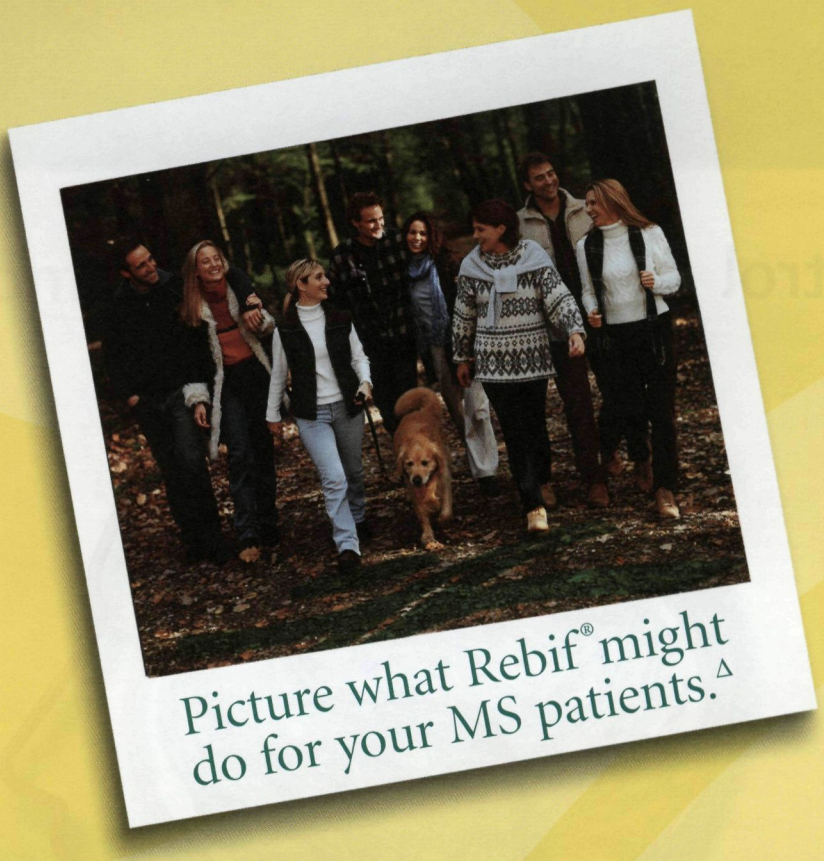

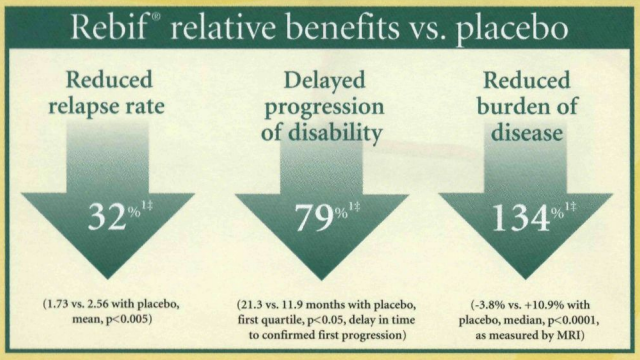

Results of the 44 mcg TIW dose at 2 years.[1]

In two pivotal studies, including a total of 628 patients, Rebif showed significant efficacy in three major outcomes (relapses, disability progression and MRI).[1,2]

Its ability to affect the course of the disease[2] has made Rebif not only a good first-line choice for relapsing-remitting MS, but the leading drug in its class.[3]

Rebif is generally well-tolerated. The most common adverse events are often manageable and decrease in frequency and severity over time.[2†]

Rebif alters the natural course of relapsing-remitting MS.[2]

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. The efficacy of Rebif has been confirmed by T_1–Gd enhanced and T_2 (burden of disease) MRI evaluations.[2]

† The most common adverse events reported are injection-site disorders (all) (92.4% vs. 38.5% placebo), upper respiratory tract infections (74.5% vs. 85.6% placebo), headache (70.1% vs. 62.6% placebo), flu-like symptoms (58.7% vs. 51.3% placebo), fatigue (41.3% vs. 35.8% placebo) and fever (27.7% vs. 15.5% placebo). Evidence of safety and efficacy derived from 2-year data only. Please see product monograph for full prescribing information.[2]

‡ Randomized, double-blind, placebo-controlled trial. Rebif 44 mcg TIW group (n=184), Rebif 22 mcg TIW group (n=189), placebo group (n=187).[1]

Δ Fictitious case may not be representative of results for the general population.

PAAB

Pr Rebif® Interferon beta-1a

serono

FOR MULTIPLE REASONS.

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