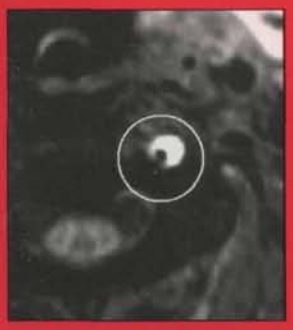
Volume 30 Number 2 May 2003

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

AN INTERNATIONAL JOURNAL / UN JOURNAL INTERNATIONAL

Mid-basilar stenosis



Neuroimaging Highlight

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

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-30, A-31

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The Canadian Neurosurgical Society
La Société Canadienne de Neurochirurgie

The Canadian Society of Clinical Neurophysiologists
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All Week Strong.

Once-A-Week

AVONEX®

Consider the Data.

MS Disability Progression: 37% reduction in the probability of disability progression over two years (21.9% vs. 34.9%; p=0.02)¶[1,2]

Annual Exacerbation Rate: 32% reduction in the annual exacerbation rate over two years (0.61 vs. 0.90; p=0.002)*[1,2]

Relapse-free Rate: 38% of patients remained relapse free at two years (p=0.03)@[1,2]

Brain Atrophy Reduction: 55% reduction in brain atrophy progression during the second year of therapy (-0.233 vs. -0.521; p=0.03)#[3]

MRI Lesions: 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]

Pr 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.

BIOGEN CANADA

PAAB

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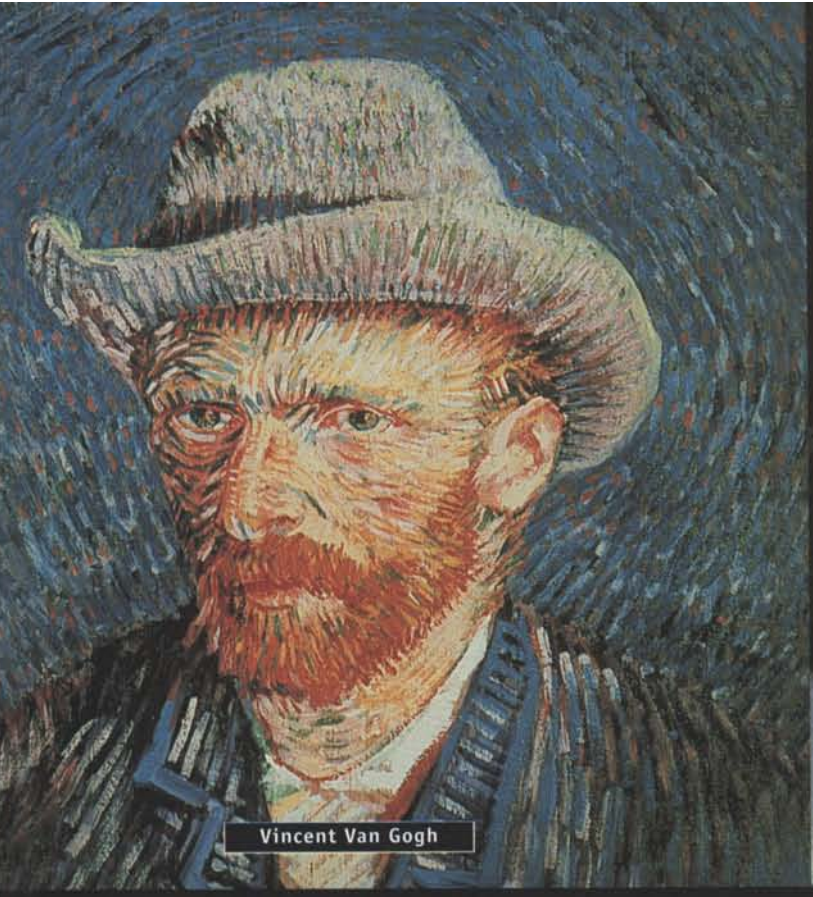
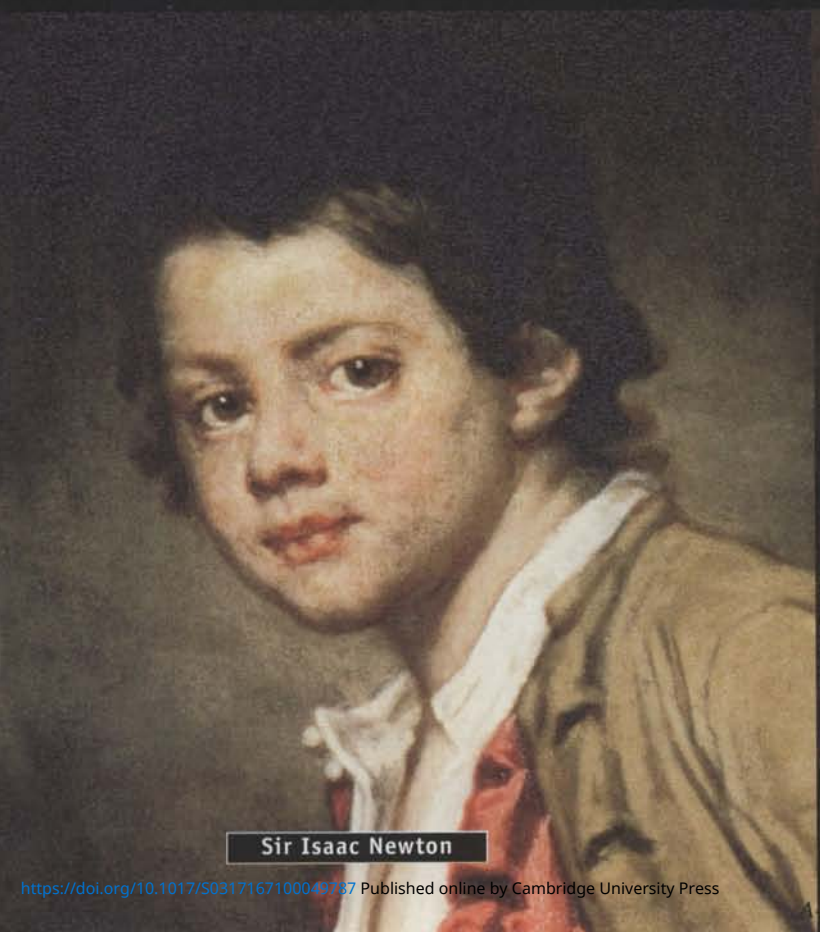
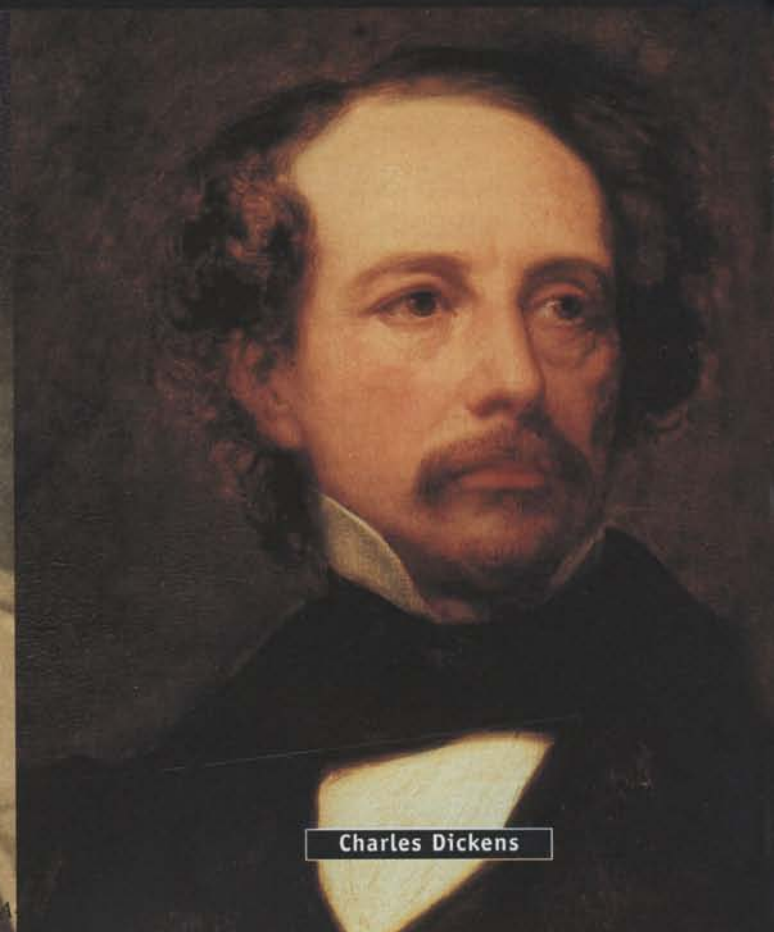
For brief prescribing information see pages A-43



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.

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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NOW BETA

"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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INTERFERON BETA-1b

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For brief prescribing information see pages A-40, A-41

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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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℗ **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 ≥85 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 Proteins:*** Drug displacement studies have been performed *in vitro* between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3 - 10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin. ***Effect of ARICEPT on the Metabolism of Other Drugs:*** *In vitro* studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50 - 130 µM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 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, restlessness. ***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%) apistaxis, 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=885) of over two years. In one of the studies, 253 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, 76% (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, hyponatremia, 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).

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See page A-11

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25 Years Ago in the Canadian Journal of Neurological Sciences

Cerebral Hemodynamics in Migraine

V.C. Hachinski, J. Olesen, J.W. Norris, B. Larsen, E. Enevoldsen and N.A. Lassen

Summary: Clinical and angiographic findings in migraine are briefly reviewed in relation to cerebral hemodynamic changes shown by regional cerebral blood flow (rCBF) studies. Three cases of migraine, studied by the intracarotid xenon 133 method during attacks, are reported.

In classic migraine, with typical prodromal symptoms, a decrease in cerebral blood flow has been demonstrated during the aura. Occasionally, this flow decrease persists during the headache phase. In common migraine, where such prodomata are not seen, a flow decrease has not been demonstrated.

During the headache phase of both types of migraine, rCBF has usually been found to be normal or in the high range of normal values. The high values may represent postischemic hyperemia, but are probably more frequently secondary to arousal caused by pain.

Thus, during the headache phase, rCBF may be subnormal, normal or high. These findings do not exclude the possibility of distension of the larger intracranial arteries during migraine headache, but the angiographic evidence, however limited, does not support this speculation.

Can. J. Neurol. Sci. 1977;4:245

Lumbo-sacral Radiculopathy Induced by Radiation

E.M. Ashenhurst, G.R.C. Quartey and A. Starreveld

Summary: Two patients had lumbo-sacral radiculopathy following radiation treatment of cancer. Twenty previously reported cases were similar. The clinical picture is one of progressive motor and sensory loss in the legs, usually appearing within a year after radiation, but sometimes delayed up to several years. Experimental studies quoted indicate greater vulnerability of peripheral nerves to ionizing radiation than has been previously recognized. Lumbo-sacral radiculopathy is readily produced in the experimental animal (rat) and affords an experimental model closely resembling the human cases reported.

Can. J. Neurol. Sci. 1977;4:259

A Community Neurologist's Personal Viewpoint on Neurological Training

Charles A. Simpson

Summary: A study of 200 patients referred to a community neurologist showed that 87.5% of the patients were seen in the office and only 12.5% in hospital. Neurological signs were present in 52% and 28.5% had neurological signs which materially affected the diagnosis. A questionnaire sent to several teaching centers showed that only one centre sent students and residents to community neurologists' offices at all and in most centers the resident spent just 10 to 20% of his time seeing out-patients. It was felt that the balance of in-patient/out-patient teaching for students and residents was wrong, and that more emphasis should be placed on the neurological history than on the examination. Proposals are made to involve the community neurologist as well as the academic neurologist in the training of students and residents which would benefit all four groups.

Can. J. Neurol. Sci. 1977;4:265

Central Nervous System Vasculitis in Rheumatoid Arthritis

Peter Watson, John Fekete and John Deck

Summary: The history of a patient with rheumatoid arthritis and necrotizing vasculitis affecting only the central nervous system is reported. Clinical and pathological involvement by this process was present in both cerebral hemispheres, the pons and spinal cord. Review of the literature revealed that cerebral vasculitis in rheumatoid arthritis has been reported rarely and spinal cord vasculitis not at all.

Can. J. Neurol. Sci. 1977;4:269

Afterdischarge Thresholds and Kindling Rates in Dorsal and Ventral Hippocampus and Dentate Gyrus

Ronald Racine, Patty A. Rose and W.M. Burnham

Summary: Electrodes were implanted into dorsal hippocampus (CA1), ventral CA1, dorsal dentate gyrus or ventral dentate gyrus. Epileptiform afterdischarge (AD) thresholds were lower in dorsal areas than in ventral areas. Dorsal areas, however, required a greater number of stimulations to develop ("kindle") a fully generalized convulsion than did ventral areas. Thresholds and kindling rates in the dentate gyrus were intermediate between dorsal and ventral CA1, except for the ventral dentate which had higher AD thresholds than ventral CA1.

Secondary sites within the hippocampus subsequently kindled within a few stimulations following completion of kindling in the primary site, regardless of which hippocampal area served as the primary site.

Can. J. Neurol. Sci. 1977;4:273

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Pour documentation voir pages A-40, A-41

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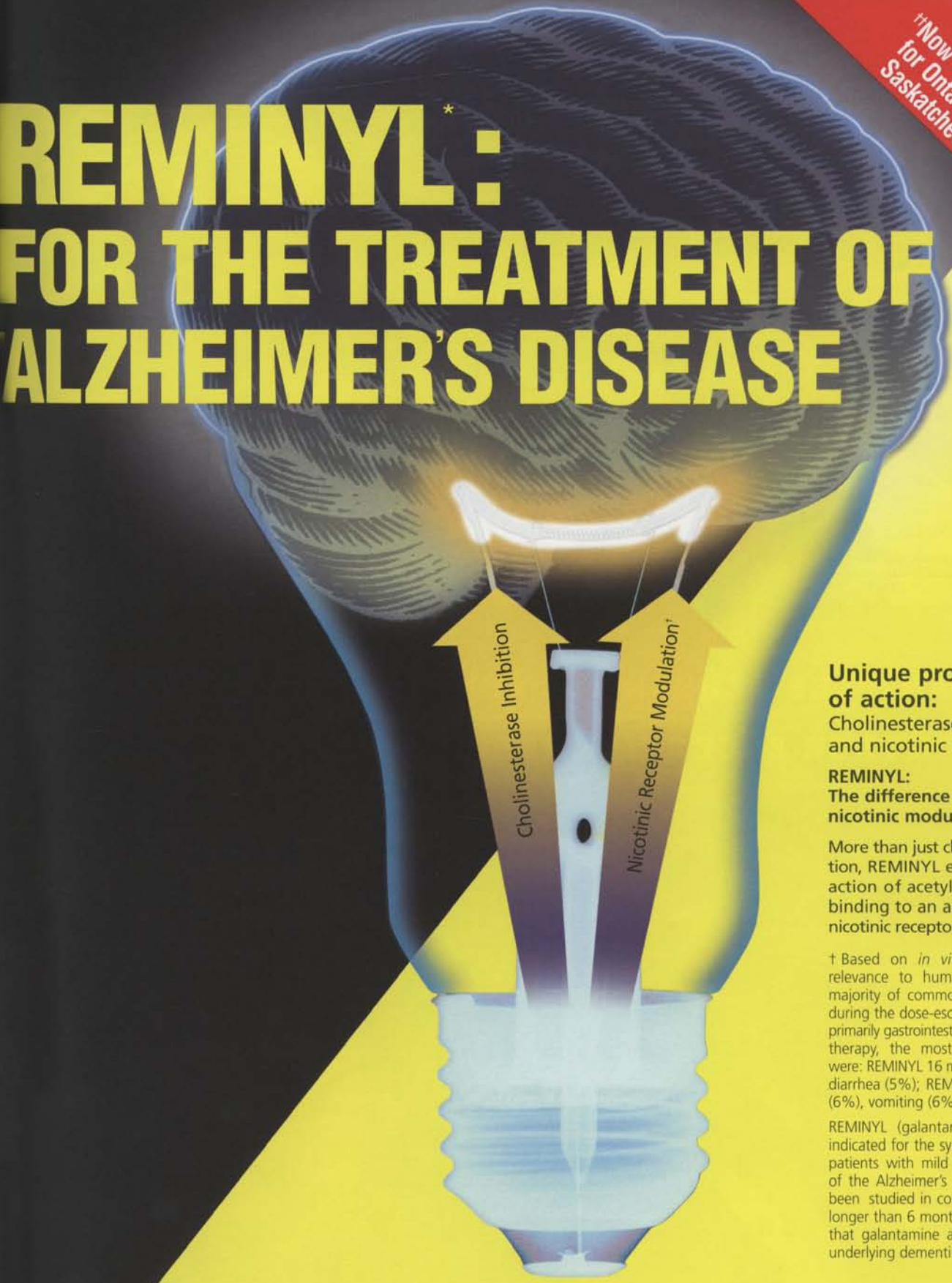

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References:
1. REMINYL* (galantamine hydrobromide) Product Monograph, JANSSEN-ORTHO Inc., March 6, 2002.
2. Maelicke A, Albuquerque EX. *Eur J Pharmacol* 2000;393:165-170.

†† Exception drug status.

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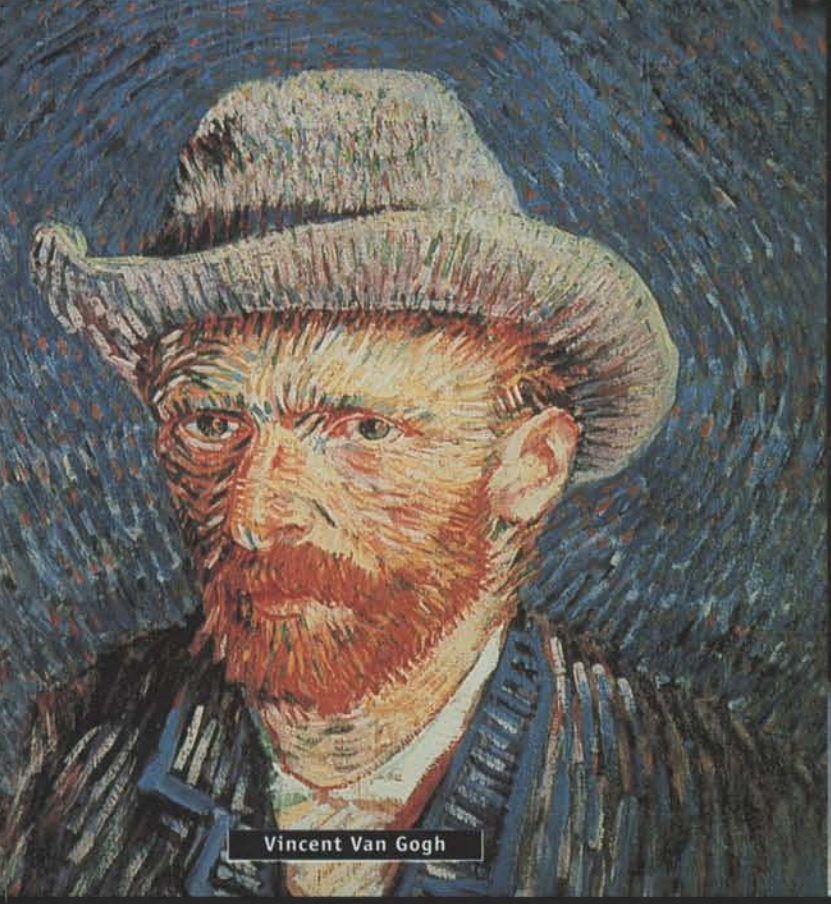

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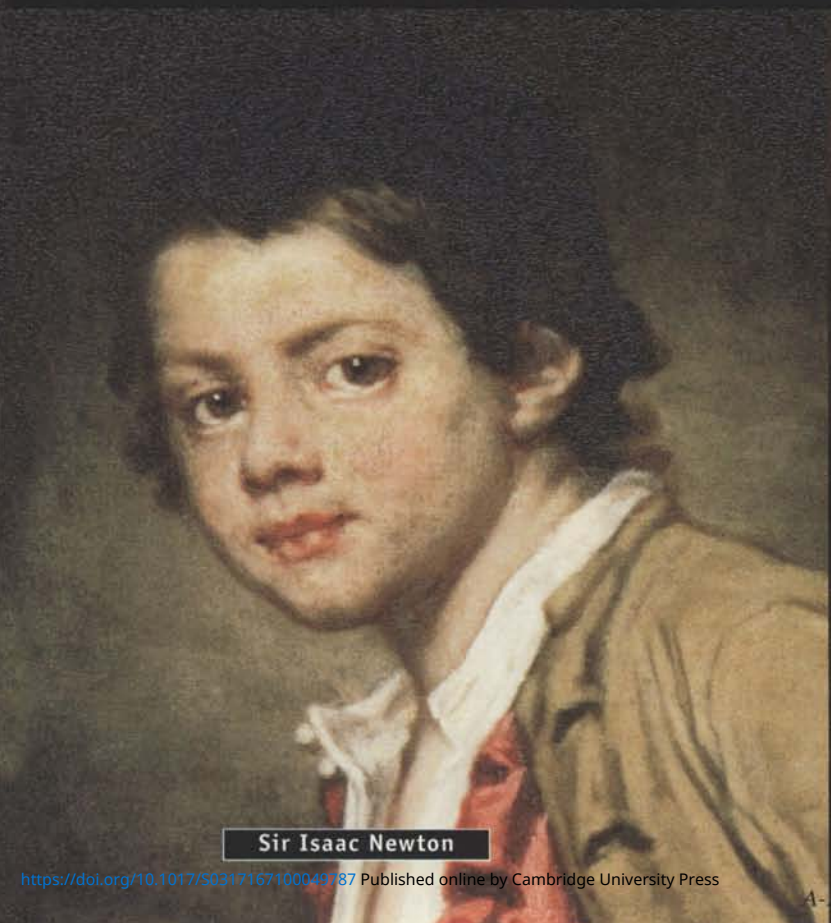

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Pour documentation voir pages A-32, A-33

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Proven Efficacy

- **Sustained mean relapse rate reduction**
  — 29% demonstrated at 2 years (1.19 vs. 1.68 with placebo, p=0.007, n=251)[1]

Reduced Irreversible Tissue Damage

- **COPAXONE® reduced development of persistent black holes by 50%**
  (15.6% vs. 31.4% with placebo at month 9, p=0.002, n=239)[2-4]*†
  *Clinical significance of these findings has not been established.

Established Safety Profile

- **Demonstrated for over 7 years in clinical trials**[5]
- **No recommended monitoring of liver and thyroid function or complete blood count**[5]

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%).

COPAXONE® is indicated for Relapsing-Remitting Multiple Sclerosis. The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.

†Black holes: MS lesions that evolve into persistent hypointense lesions on postcontrast T1-weighted images.

COPAXONE®
(glatiramer acetate injection)
Efficacy backed by evidence.

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REQUIP® ropinirole

Rethinking Parkinson's.

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.

CONTRAINDICATIONS

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

WARNINGS

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 and should be informed of this risk. **Hallucinations** – In controlled trials, REQUIP (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group) and in 10.1% of patients receiving REQUIP and levodopa (4.2% receiving placebo and levodopa). Hallucination was of sufficient severity that it led to discontinuation in 1.3% and 1.9% of patients during early and adjunct therapy, respectively. The incidence of hallucination was dose-dependent both in early and adjunct therapy studies.

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. **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. 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 (see Pharmacokinetics). 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** – As orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP therapy patients should be cautioned not to drive a motor vehicle or operate potentially hazardous machinery until they are reasonably certain that REQUIP therapy does not affect their ability to engage in such activities.

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 1 lists adverse events that occurred at an incidence of 2% 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. The Adverse Reactions section has been condensed. See full Product Monograph for the complete information.

DOSAGE AND ADMINISTRATION

REQUIP (ropinirole hydrochloride) should be taken three times daily. While administration of REQUIP with meals may improve gastrointestinal tolerance, REQUIP may be taken with or without food. The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis up to 24 mg per day. Doses greater than 24 mg/day have not been tested in clinical trials. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms. In clinical trials, initial benefits were observed with 3 mg/day and higher doses.

	Week			
	1	2	3	4
Unit Dose (mg)	0.25	0.5	0.75	1.0
Total Daily Dose (mg)	0.75	1.5	2.25	3.0

TABLE 1

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

	Early Therapy		Adjunct Therapy	
	REQUIP N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP N = 208 % 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
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
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
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
Saliva Increased	–	–	2.4	0.8
Dysphagia	1.3	0.0	2.4	0.8
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	–	–	2.4	0.8
Musculoskeletal System				
Arthralgia	–	–	6.7	5.0
Arthritis	–	–	2.9	0.8
Psychiatric				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	–	–	6.3	3.3
Confusion	5.1	1.4	8.7	1.7
Hallucination	5.1	1.4	10.1	4.2
Nervousness	–	–	4.8	2.5
Yawning	3.2	0.0	–	–
Amnesia	2.5	1.4	4.8	0.8
Dreaming Abnormal	–	–	2.9	1.7
Red Blood Cell				
Anemia	–	–	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	–	–
Resistance Mechanism				
Upper Respiratory Tract Infection	–	–	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
Respiratory System				
Pharyngitis	6.4	4.1	–	–
Rhinitis	3.8	2.7	–	–
Sinusitis	3.8	2.7	–	–
Dyspnea	3.2	0.0	2.9	1.7
Bronchitis	2.5	1.4	–	–
Urinary System				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	–	–
Vision				
Vision Abnormal	5.7	3.4	–	–
Eye Abnormality	3.2	1.4	–	–

*: Incidence of adverse event <1%.

When REQUIP is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with REQUIP has been observed. REQUIP should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of REQUIP. *Renal and Hepatic Impairment:* In patients with mild to moderate renal impairment, REQUIP may be titrated in the recommended manner according to clinical response. Patients with severe renal impairment or on hemodialysis have not been studied and administration of REQUIP to such patients is not recommended. Patients with hepatic impairment have not been studied and administration of REQUIP to such patients is not recommended. *Estrogen Replacement Therapy:* 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 started during treatment with REQUIP, adjustment of the REQUIP dosage may be required.

AVAILABILITY OF DOSAGE FORM

REQUIP is supplied as a pentagonal film-coated Tiltab® tablet with beveled edges containing ropinirole (as ropinirole hydrochloride) as follows: 0.25 mg – white imprinted with SB and 4890; 1.0 mg – green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – blue tablets imprinted with SB and 4894. REQUIP is available in bottles in the pack size of 100 tablets. It is also available in 0.25 mg as a single unit blister pack of 21 tablets.

Full Product Monograph available to practitioners upon request.

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2. Schrag AE, *et al.* The Safety of Ropinirole, a selective non-ergoline dopamine agonist in patients with Parkinson's disease. *Clin Neuropharmacol* 1998;21:169-175.

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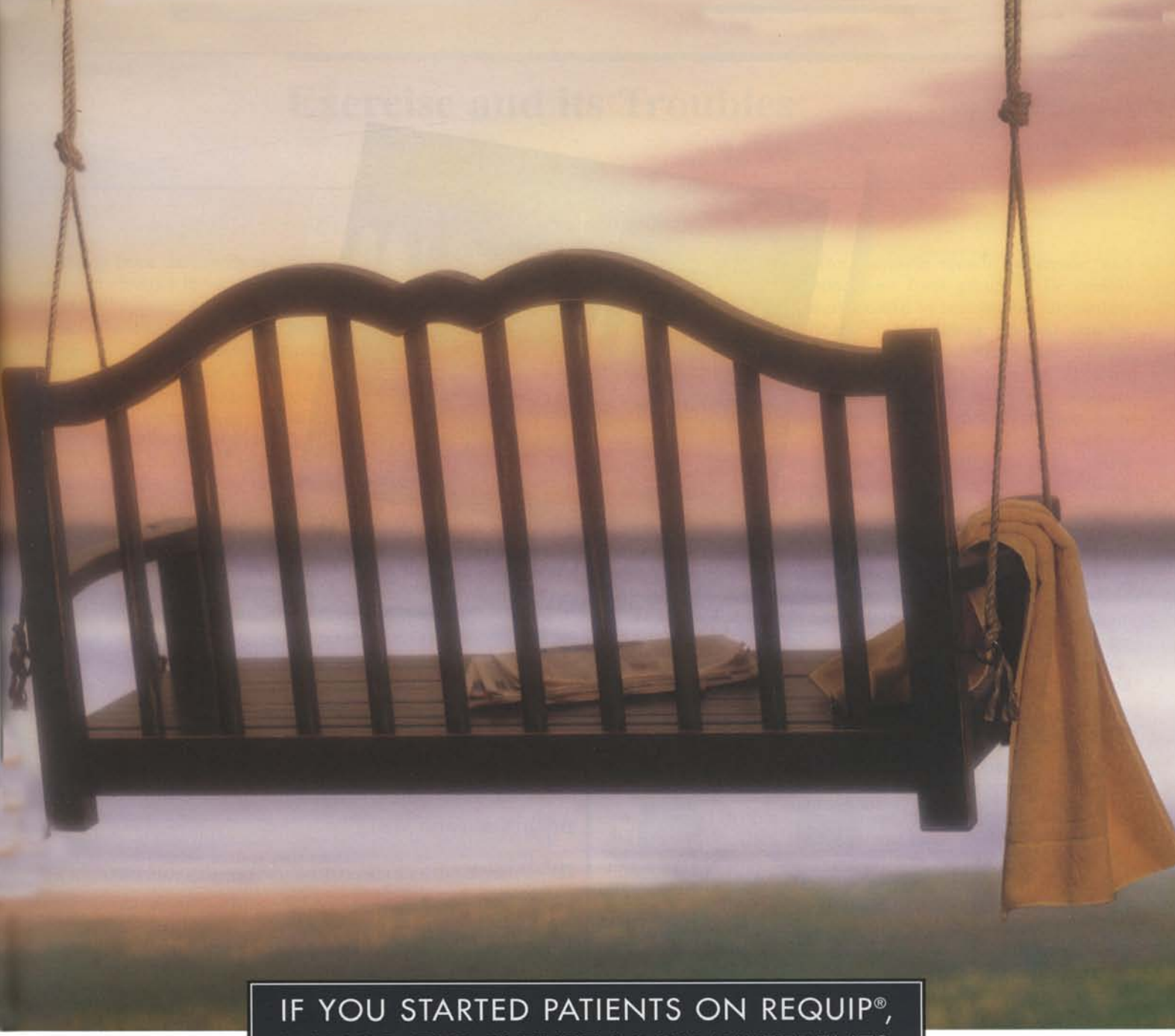

IF YOU STARTED PATIENTS ON REQUIP®, WOULD THE FUTURE LOOK DIFFERENT?

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.[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.

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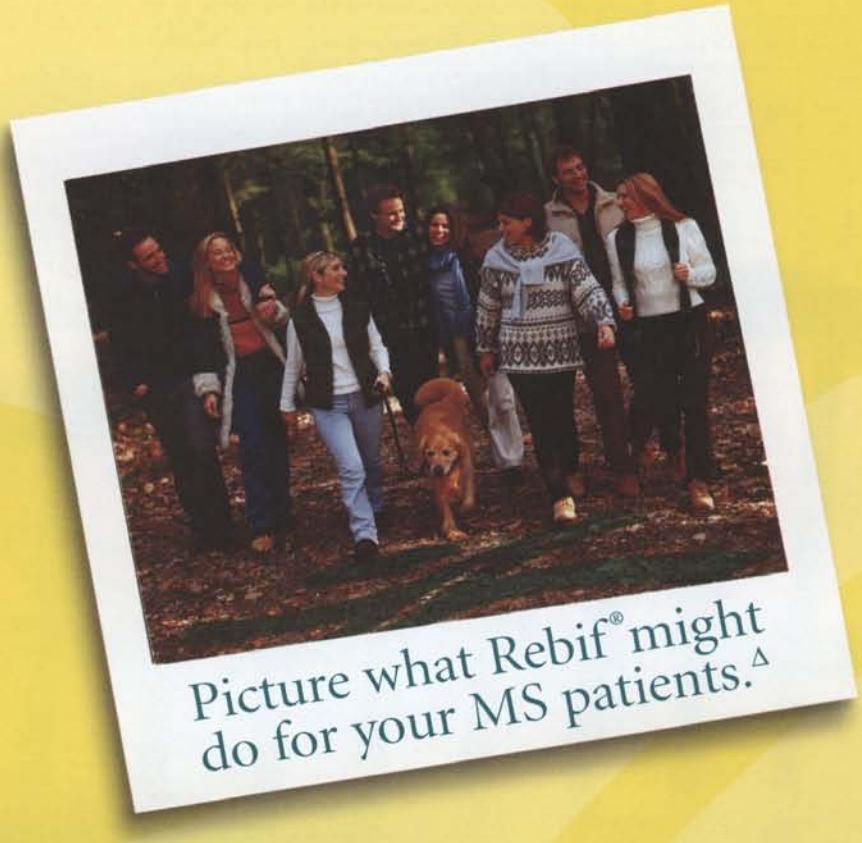
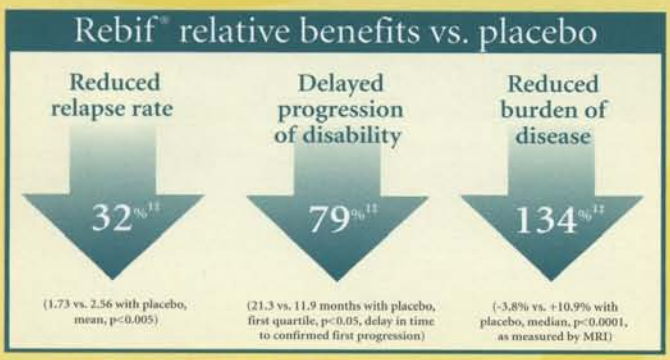


Picture what Rebif® might do for your MS patients.Δ



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.

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Pr Rebif® Interferon beta-1a

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FOR MULTIPLE REASONS.

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