Volume 22 Number 1 February 1995

THE CANADIAN JOURNAL OF Neurological Sciences

LE JOURNAL CANADIEN DES Sciences Neurologiques

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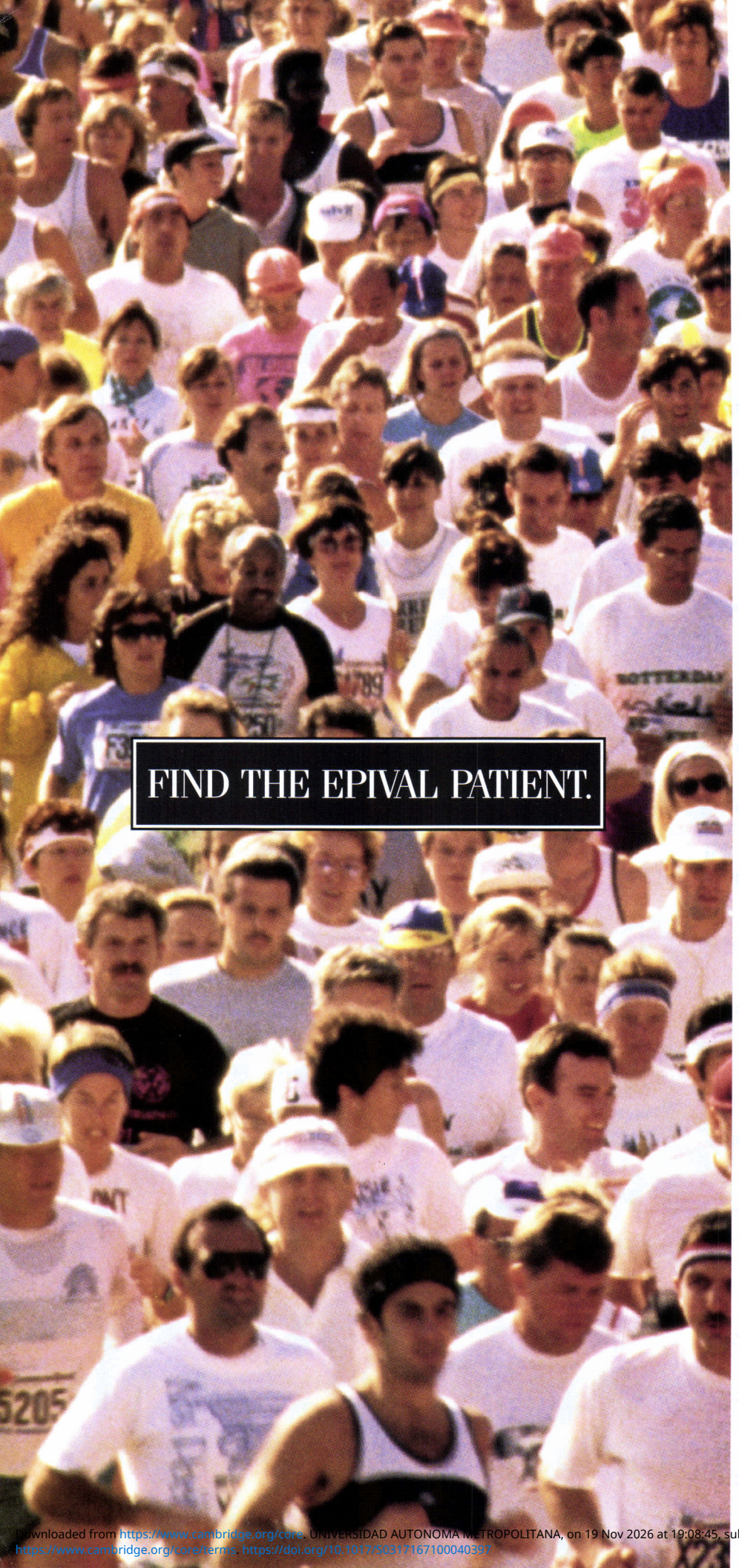
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For brief prescribing information see page xx, xxi.

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* Veuillez consulter la rubrique Précautions dans la monographie.

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If one more walks away from

The risk of stroke is greatest within the year following a TIA.[1] So it's worth knowing that a large multicentre trial showed Ticlid prevented non-cardiogenic thromboembolic stroke twice as effectively as ASA.[2] That meant relative to ASA, Ticlid saved three more patients out of every one hundred treated from a potentially crippling or life-threatening stroke.[2]

In long-term prospective randomized trials, only Ticlid has been proven effective in women as well as in men for the prevention of recurrent and initial stroke.[3,4] ASA has not been proven to reduce the rate of recurrent stroke.[5] Nor has ASA been proven to prevent initial stroke in women.[6]

Gastrointestinal complaints such as diarrhea can be limited by taking Ticlid with full meals.[7] A temporary reduction in dose may also resolve this complaint.[3,8]



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TIA patient stroke, it's worth it.

If rash occurs, discontinue therapy and rechallenge. Many rashes will not recur.[7]

In clinical trials there was a 2.4% incidence of neutropenia. Upon immediate discontinuation of therapy, the neutrophil count usually returned to normal within 1 to 3 weeks. White blood cell monitoring is required every two weeks for the first three months starting at baseline.[7]

Ticlid. Possibly the best opportunity a TIA patient has to walk away from stroke.

Turn the page and judge for yourself. Four independent studies attest to the value of Ticlid.



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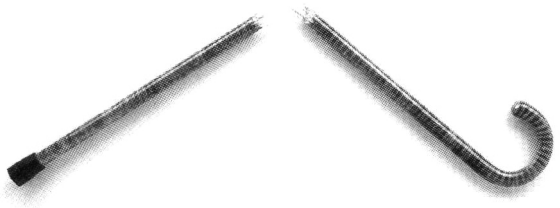
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Four major studies establish the superior efficacy of Ticlid.

Ticlopidine Versus Aspirin for Stroke Prevention: On-Treatment Results from the Ticlopidine Aspirin Stroke Study Group

J. D. Easton, Chair, TASS Publications Committee
J Stroke Cerebrovasc Dis. Vol. 3 No. 3. 1993;3:168-176.

Ticlopidine is the newest antiplatelet agent that has been compared with aspirin for stroke prevention. Results from the intent-to-treat analysis of the Ticlopidine Aspirin Stroke Study, a randomized, triple-blind trial, showed ticlopidine to be more effective than aspirin for the prevention of threatened stroke. We present the on-treatment analysis from this study in 3,034 eligible patients receiving either ticlopidine (500 mg daily) or aspirin (1,300 mg daily). Follow-up was for 2-6 years.

During year 1, the high-risk period for stroke in patients with threatened stroke, ticlopidine reduced the risk of stroke over aspirin by 48% ($p = 0.0004$: the event rates were 3.4 and 6.4 respectively). The overall risk for fatal and non fatal stroke was 27% (95% confidence intervals were 6.6 and 42.3), less with ticlopidine than with aspirin. Ticlopidine significantly decreased the risk of fatal and non fatal stroke in both sexes and has a different adverse effect profile than aspirin. More adverse effects, primarily diarrhea and rash, were reported with ticlopidine.

Stroke Prevention in Women: Role of Aspirin Versus Ticlopidine

Linda A. Hershey, M.D., Ph.D., Buffalo, New York
September 1991 *The American Journal of Medicine* Vol. 91;288-292.

Summary and Conclusions: Stroke remains an important health care problem. Although the incidence of stroke and stroke mortality is lower in women than in men, the outcome in terms of major disability, decreased quality of life, economic burdens, and impact on family life is just as real for women as for men. Although aspirin has proven efficacy for preventing initial stroke, it may have limited efficacy in preventing recurrent stroke. Moreover, questions remain about the efficacy of aspirin for stroke prevention in women. There is a need for an alternative to aspirin in stroke prevention therapy.

Ticlopidine has demonstrated efficacy for both initial and recurrent stroke prevention and has been shown to be more effective than aspirin for patients at high risk for a first stroke. It is just as effective for stroke prevention in women as in men. The overall incidence of adverse effects seen with ticlopidine is not significantly different from that seen with aspirin, although careful hematologic monitoring is required with ticlopidine during the first 3 months of use. Both agents are important tools to use in addition to antihypertensive therapy and smoking cessation in stroke prevention.

Ticlopidine Versus Aspirin for the Prevention of Recurrent Stroke
Analysis of Patients With Minor Stroke From the Ticlopidine Aspirin Stroke Study

John W. Harbison. M.D., for the Ticlopidine Aspirin Stroke Study Group
Stroke 1992:1723-1727.

Background and Purpose: Ticlopidine has not been formally compared with aspirin in patients with a completed stroke. We therefore performed an analysis on a subgroup of patients from the Ticlopidine Aspirin Stroke Study (TASS) with a recent minor completed stroke as the qualifying ischemic event.

Methods: This was a multicenter, double-blind, randomized trial of patients with a recent history of cerebral ischemia. Eligible patients had a qualifying minor stroke within 3 months of study entry. All patients received either 650 mg aspirin twice daily or 250 mg ticlopidine twice daily for up to 5.8 years. The primary study end point was the first occurrence of non fatal stroke or death from any cause. A secondary end point was the first occurrence of a fatal or non fatal stroke.

Results: Minor stroke was the qualifying ischemic event in 927 patients (463 received ticlopidine and 464 received aspirin). The cumulative event rate at 1 year for non fatal stroke or death was 6.3% for patients receiving ticlopidine and 10.8% for patients receiving aspirin, a 42% risk reduction in favour of ticlopidine. For fatal or non fatal stroke, the cumulative event rate at 1 year was 4.8% for patients receiving ticlopidine and 7.5% for those receiving aspirin, a risk reduction of 36% for ticlopidine relative to aspirin. The overall risk reductions were 22.1% for non fatal stroke or death and 19.9% for fatal or non fatal stroke. Adverse reactions were reported in 58% of the ticlopidine patients and 51% of the aspirin patients.

Conclusions: The results in this subgroup are consistent with the overall TASS results and show that ticlopidine is somewhat more effective than aspirin for reducing the risk of stroke in patients with a completed minor stroke.

The Canadian American Ticlopidine Study (CATS) in Thromboembolic Stroke

Gent, J., et al. *The Lancet:* Saturday 3 June 1989.

The Canadian American Ticlopidine Study (CATS) is a randomised, double-blind placebo-controlled trial to assess the effect of ticlopidine (250 mg twice daily) in reducing the rate of subsequent occurrence of stroke, myocardial infarction, or vascular death in patients who have had a recent thromboembolic stroke. Twenty-five centres entered 1,072 patients into the study between 1 week and 4 months after their qualifying stroke. The patients were treated and followed up to 3 years (mean 24 months). In the efficacy analysis, the event rate per year for stroke, myocardial infarction or vascular death, considered together, was 15.3% in the placebo group and 10.8% in the ticlopidine group, representing a relative risk reduction with ticlopidine of 30.2% (95% confidence interval 7.5-48.3%; p=0.006). Ticlopidine was beneficial for both men and women (relative risk reductions 28.1%, p=0.037, and 34.2%, p=0.045, respectively). Analysis by intention-to-treat gave a smaller estimate of risk reduction (23.2%, p=0.020) for stroke, myocardial infarction, or vascular death. Adverse experiences associated with ticlopidine included neutropenia (severe in about 1% of cases) and skin rash and diarrhea (severe in 2% of cases each); all were reversible.

This study provides evidence of a beneficial effect of ticlopidine in both men and women with a recent thromboembolic stroke.

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THERAPEUTIC CLASSIFICATION Inhibitor of Platelet Function

ACTION Ticlid (ticlopidine hydrochloride) is an inhibitor of platelet aggregation. It causes a time and dose-dependent inhibition of platelet aggregation and release of platelet factors, as well as a prolongation of bleeding time. The drug has no significant *in-vitro* activity.

The exact mechanism of action is not fully characterized, but does not involve inhibition of the prostacyclin/thromboxane pathways or platelet cAMP.

Ticlid interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect of Ticlid on platelet function is irreversible.

Template bleeding time is usually prolonged by two to five-fold of baseline values with the therapeutic dose of Ticlid.

Upon discontinuation of Ticlid dosing, bleeding time and other platelet function tests return to normal within one week in the majority of patients.

The correlation between ticlopidine hydrochloride plasma levels and activity is still under investigation. Much of the following data was obtained from older patients corresponding to the age of patients participating in clinical trials (mean age: 63 years).

After oral administration of the therapeutic dose of Ticlid, rapid absorption occurs, with peak plasma levels occurring at approximately 2 hours after dosing. Absorption is at least 80% complete. Administration of Ticlid after meals results in an increased (20%) level of ticlopidine hydrochloride in plasma.

Steady state plasma levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 days of dosing at 250 mg BID. The terminal elimination half-life is 4-5 days. However, inhibition of platelet aggregation is not correlated with plasma drug levels.

Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins in a non-saturable manner.

Ticlopidine hydrochloride is metabolized extensively by the liver; no intact ticlopidine hydrochloride is detected in the urine. Unmetabolized ticlopidine hydrochloride is a minor component in plasma after a single dose, but at steady state, ticlopidine hydrochloride is the major component.

Impaired hepatic function resulted in higher than normal plasma levels of unchanged ticlopidine hydrochloride after single doses or after multiple doses.

Inhibition of platelet aggregation is detected within 2 days of administration with 250 mg BID. Maximum platelet aggregation inhibition is achieved 8 to 11 days following dosing with 250 mg BID.

INDICATIONS AND CLINICAL USE Ticlid (ticlopidine hydrochloride) tablets are indicated for reduction of the risk of first or recurrent stroke for patients who have experienced at least one of the following events: Complete Thromboembolic Stroke, Minor Stroke, Reversible Ischemic Neurological Deficit (RIND), or Transient Ischemic Attack (TIA) including Transient Monocular Blindness (TMB).

Considerations in the selection of stroke prevention therapy should include the patient's current medical status and history, and their ability to comply with the required blood monitoring instructions concerning the use of ticlopidine.

CONTRAINDICATIONS Ticlid (ticlopidine hydrochloride) is contraindicated in the following conditions: 1. Known hypersensitivity to drug or its excipients. 2. Presence of haematopoietic disorders (such as neutropenia and/or thrombocytopenia). 3. Presence of haemostatic disorder. 4. Conditions associated with active bleeding, such as bleeding peptic ulcer or intracranial bleeding. 5. Severe liver dysfunction.

WARNINGS The following warnings were developed from clinical trial experience with over 2000 patients with cerebrovascular disease who were treated with ticlopidine for as long as 5.8 years.

Neutropenia and Thrombocytopenia: About 2.4% of ticlopidine-treated patients in clinical trials developed neutropenia (defined as an absolute neutrophil count (ANC) below 1.2×10^9 cells/L). The incidence of severe neutropenia (ANC<0.45×10^9 cells/L) was 0.8%. Severe neutropenia occurs during the first 3-12 weeks of therapy, and may develop quickly over a few days. The bone marrow shows a reduction in myeloid precursors. The condition may be life-threatening. It is usually reversible, and the recovery occurs within 1-3 weeks after discontinuation of the drug but may take longer, on occasion.

In clinical trials, thrombocytopenia (defined as a platelet count of $<0.8 \times 10^{11}$ cells/L) has been observed in 0.4% of ticlopidine patients. The incidence of thrombocytopenia in patients on ASA or placebo was 0.3% or 0.4% respectively. The thrombocytopenia may occur as an isolated finding or in combination with neutropenia. Thrombocytopenia occurs during the first 3-12 weeks of therapy, and recovery usually occurs after drug discontinuation.

All patients should have a white blood cell count with a differential and platelet count performed every 2 weeks starting at baseline, before treatment is initiated, to the end of the third month of therapy with Ticlid. When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the values should be confirmed. If the presence of neutropenia (ANC $<1.2 \times 10^9$ cells/L) or thrombocytopenia ($<0.8 \times 10^{11}$ cells/L), are confirmed, the drug should be discontinued. Because of the long plasma half-life of Ticlid, it is recommended that any patient who discontinues Ticlid for any reason within the first 90 days have an additional CBC with white cell differential count obtained two weeks after discontinuation of therapy. (See PRECAUTIONS.)

Rarely, cases of pancytopenia, aplastic anemia or thrombocytopenia, have been reported. Most cases were reversible, but some of them have been fatal. Thrombocytopenia may occur in isolation or together with neutropenia. Thrombotic thrombocytopenic purpura (TTP) has been reported, therefore careful attention to diagnosis should be made to guide treatment, platelet transfusion may be harmful in these patients.

Hemorrhagic Complications: Prolongation of bleeding time occurs in subjects treated with Ticlid. Purpura and a few cases of more serious hemorrhagic events such as hematemesis, melena, hemothorax and intracranial bleeding have been reported. Patients must be instructed to watch for signs of bleeding disorders and to report any abnormality to their physician immediately. Ticlid therapy has to be stopped by the patient if a physician is not immediately available for consultation.

Anticoagulant Drugs: Should be avoided as tolerance and safety of simultaneous administration with Ticlid has not been established.

Hepatic Abnormalities: Most patients receiving ticlopidine hydrochloride showed some increase of their alkaline phosphatase values above their baseline and in one-third the increase exceeded the upper reference range. In 6% the value was greater than twice the upper reference range. These increases in alkaline phosphatase were nonprogressive and asymptomatic. In clinical trials, two cases (0.1%) of cholestatic jaundice accompanied by elevated transaminases alkaline phosphatase, and bilirubin levels above 43 µmol/L have been observed. Both patients recovered promptly upon drug discontinuation.

Pregnancy: The safety of Ticlid in pregnancy has not been established. It should not be used in pregnant patients.

Pediatric Use: Safety in children has not been studied. Do not use in pediatric patients.

PRECAUTIONS

Selection of Patients: Ticlid should be used only for the established indications (see INDICATIONS) and should not be given to patients with haematopoietic disorders, haemostatic disorders, patients suffering from conditions associated with active bleeding (see CONTRAINDICATIONS) and patients anticipating elective surgery. In clinical trials elderly patients tolerated the drug well, but safety in children and pregnant women has not been established.

Clinical Monitoring: All patients have to be carefully monitored for clinical signs and symptoms of adverse drug reactions (see ADVERSE REACTIONS). The signs and symptoms possibly related to neutropenia (fever, chills, sore throat, ulcerations in oral cavity), thrombocytopenia and abnormal hemostasis (prolonged or unusual bleeding, bruising, purpura, dark stool), jaundice (including dark urine, light coloured stool) and allergic reactions should be explained to the patients who should be advised to stop medication and consult their physician immediately if any of these occur.

Laboratory Monitoring: All patients should have a white blood cell count with a differential and a platelet count performed every 2 weeks starting at baseline, before treatment is initiated, to the end of the third month of therapy with Ticlid. When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the value should be confirmed. If the presence of neutropenia (ANC $<1.2 \times 10^9$ cells/L) or thrombocytopenia ($< 0.8 \times 10^{11}$ cells/L) are confirmed, the drug should be discontinued. Because of the long plasma half-life of Ticlid, it is recommended that any patient who discontinues Ticlid for any reason within the first 90 days have an additional CBC with white cell differential obtained two weeks after discontinuation of therapy (see WARNINGS). Thereafter, the WBC counts need only be repeated for symptoms or signs suggestive of neutropenia. Liver function tests should be conducted during therapy with Ticlid (ticlopidine hydrochloride) in response to signs and symptoms suggestive of hepatic dysfunction.

Elective Surgery: Ticlid should be discontinued 10 to 14 days prior to elective surgery or dental extraction and bleeding time and thrombocyte count performed before the procedure if clinically indicated.

Emergency Surgery: Prolonged bleeding during surgery may be a problem in ticlopidine-treated patients. Transfusions of fresh platelets would be expected to improve haemostasis in such patients, but there are no data from clinical trials to confirm this expectation. There are data from clinical pharmacology trials that indicate treatment with glucocorticosteroids can normalize bleeding time in ticlopidine-treated subjects, but there is no experience with ticlopidine-treated surgical patients to show that such treatment improves haemostasis.

Specific Precautions: Liver: Ticlid is contraindicated in patients with severe liver dysfunction or cholestatic jaundice. Mild increase of alkaline phosphatase may be seen for the duration of the treatment and is inconsequential in the majority of patients (see WARNINGS and CONTRAINDICATIONS).

Kidneys: Ticlid has been well tolerated in patients with moderately decreased renal function. In severe renal disease, caution and close monitoring are recommended.

Gastrointestinal System: Conditions associated with active bleeding, such as bleeding ulcers, constitute contraindication for Ticlid. Clinical judgement and monitoring of stool for occult blood are required for patients with a history of ulcerative lesions. Trauma: Ticlid should be discontinued temporarily until the danger of abnormal bleeding is eliminated. A single fatal case of intracranial bleeding following head trauma has been reported. The extent to which Ticlid may have contributed to the severity of the bleeding is unknown.

Drug Interactions: The following table outlines the agents which have been concomitantly administered with ticlopidine hydrochloride and the observed interaction (if any):

AGENTS	OBSERVED INTERACTION
Acetylsalicylic acid (ASA)	Potentiation of ASA's effect on collagen-induced platelet aggregation (see WARNINGS).
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in $t^1/_2$ of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride.
Theophylline	$t^1/_2$ of theophylline increased from 8.6 to 12.2 hr along with a comparable reduction in its total plasma clearance.
Digoxin	Approximately 15% reduction in digoxin plasma levels (little or no change in digoxin's efficacy expected).
Cimetidine	Chronic administration of cimetidine induced a 50% reduction in clearance of a single dose of ticlopidine hydrochloride.
Antacids	20% decrease in ticlopidine plasma level when administered after antacids.
Phenobarbital	No interaction reported.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, Ticlid was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (however see WARNINGS) without evidence of clinically significant adverse interactions.

ADVERSE REACTIONS Most adverse effects are mild, transient and occur early in the course of treatment.

In controlled clinical trials of 1 to 5 years duration, discontinuation of Ticlid (ticlopidine hydrochloride) due to one or more adverse effects was required in 20.9% of patients. In these same trials, ASA and placebo led to discontinuation in 14.5% and 6.7% of patients respectively. The incidence rates of adverse reactions listed in the following table were derived from multicenter, controlled clinical trials comparing ticlopidine HCl, placebo, and ASA over study periods of up to 5 years. The rates are based on adverse reactions considered probably drug-related by the investigator. Adverse experiences occurring in greater than one percent of patients treated with Ticlid in controlled clinical trials are shown in the Table below.

PERCENT OF PATIENTS IN CONTROLLED STUDIES

	Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence		Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence
Event							
Diarrhea	12.5(6.3)*	5.2(1.8)	4.5(1.7)	Nausea	7.0(2.6)	6.2(1.9)	1.7(0.9)
Dyspepsia	7.0(1.1)	9.0(2.0)	0.9(0.2)	Rash	5.1(3.4)	1.5(0.8)	0.6(0.9)
GI Pain	3.7(1.9)	5.6(2.7)	1.3(0.4)	Neutropenia	2.4(1.3)	0.8(0.1)	1.4(0.4)
Purpura	2.2(0.2)	1.6(0.1)	0.0(0.0)	Vomiting	1.9(1.4)	1.4(0.9)	0.9(0.4)
Flatulence	1.5(0.1)	1.4(0.3)	0.0(0.0)	Pruritus	1.3(0.8)	0.3(0.1)	0.0(0.0)
Dizziness	1.1(0.4)	0.5(0.4)	0.0(0.0)	Anorexia	1.0(0.4)	0.5(0.4)	0.0(0.0)

* Percent of patients (in parentheses) discontinuing clinical trials due to event.

The incidence of thrombocytopenia in these controlled studies was 0.4% in the Ticlid and placebo groups of patients and 0.3% in the ASA patient population.

The following rare events have been reported and their relationship to Ticlid is uncertain.

Pancytopenia, hemolytic anemia with reticulocytosis, thrombocytopenic thrombotic purpura, jaundice, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, nephrotic syndrome, myositis, and hyponatremia.

Gastrointestinal: Ticlid therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild and transient in nature and occur within 3 months of initiation of therapy. Typically, events are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued.

Hemorrhagic: Ticlid has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding, and postoperative bleeding.

Intracerebral bleeding was rare in clinical trials with Ticlid, and was no more than that seen with comparator agents (ASA, placebo).

Rash: Ticlopidine hydrochloride has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean time to onset of 11 days. If drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of more severe rashes.

Altered Laboratory Findings: Hematological: Neutropenia and rarely thrombocytopenia have been associated with Ticlid administration (see WARNINGS).

Liver: Ticlid therapy has been associated with elevations of alkaline phosphatase (See WARNINGS). Maximal changes occur within 1-4 months of therapy initiation. No further progressive increases are seen with continuous therapy. Occasionally patients developed deviations in bilirubin and SGOT.

Cholesterol: Chronic Ticlid therapy has been associated with increased serum cholesterol and triglycerides. Serum levels of HDL-C, LDL-C, VLDL-C, and triglycerides are increased 8-10% after 1-4 months of therapy. No further progressive elevations are seen with continuous therapy. The ratios of the lipoprotein subfractions are unchanged. The effect is not correlated with age, sex, alcohol use, or diabetes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE One case of deliberate overdosage with Ticlid (ticlopidine hydrochloride) has been reported in a foreign postmarketing surveillance program. A 38-year-old male took a single 6000 mg dose of Ticlid (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Based on animal studies, overdosage may result in severe gastrointestinal intolerance.

In the case of excessive bleeding after injury or surgery, standard supportive measures should be carried out if indicated, including gastric lavage, platelet transfusion and use of corticosteroids.

DOSAGE AND ADMINISTRATION The recommended dose of Ticlid (ticlopidine hydrochloride) is 250 mg twice daily with food. Ticlid should be taken with meals to minimize gastrointestinal intolerance.

PHARMACEUTICAL INFORMATION

(i) Drug Substance

Description: Ticlopidine hydrochloride is a white crystalline solid. It is freely soluble in water and self buffers to a pH of 3.6. It also dissolves freely in methanol, is sparingly soluble in buffer solutions above pH 6.0, methylene chloride and ethanol, and is slightly soluble in acetone.

(ii) Composition: Ticlopidine hydrochloride tablets are provided, as white film coated tablets containing ticlopidine hydrochloride, citric acid, povidone, micro-crystalline cellulose, corn starch, stearic acid powder, magnesium stearate and water. The coating suspension consists of hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol. The ink for printing contains D&C yellow #10 aluminum lake and FD&C blue #1 aluminum lake.

(iii) Stability and Storage Recommendations: Store at room temperature. Ticlid tablets should be dispensed in light resistant containers. Blister packs should not be exposed to light.

AVAILABILITY Ticlid 250 mg tablets are oval white film coated tablets printed using green ink with Ticlid above half an arrow on one side, "250" above half an arrow on the other side. The tablets are available in a fold-over card of 28 tablets (2 blisters of 14 tablets). They are also available in boxes of 56 (4 x 14) tablets and 168 (12 x 14) tablets.

For the first 3 months of therapy, only request or dispense the 14 days supply of tablets (see PRECAUTIONS).

Product Monograph available to Health Professionals on request.

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INFORMATION FOR AUTHORS

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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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For brief prescribing information see pages xvii, xix.

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P SINEMET® CR 200/50 100/25

(levodopa/carbidopa) CONTROLLED-RELEASE

Controlled-Release Tablets

Antiparkinson Agent

Indications and Clinical Use: SINEMET® CR (levodopa and carbidopa) is indicated for the treatment of Parkinson's disease.

At this time, experience in patients not previously treated with levodopa/decarboxylase inhibitors or levodopa alone is limited.

SINEMET® CR is not recommended for the treatment of drug-induced extrapyramidal reactions.

Contraindications: Monoamine oxidase inhibitors (except low doses of selective MAO-B inhibitors) and SINEMET® CR (levodopa and carbidopa) should not be given concomitantly. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET® CR.

SINEMET® CR should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.

As with levodopa, SINEMET® CR should not be given when administration of a sympathomimetic amine is contraindicated.

SINEMET® CR is contraindicated in patients with known hypersensitivity to any component of this medication.

Because levodopa may activate a malignant melanoma, SINEMET® CR should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

Warnings: When patients are receiving levodopa monotherapy or SINEMET® (levodopa and carbidopa), this medication must be discontinued at least 8 hours before therapy with SINEMET® CR is started. (For appropriate dosage substitutions, see DOSAGE AND ADMINISTRATION).

As with levodopa or SINEMET®, SINEMET® CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. These adverse reactions may be more prolonged with SINEMET® CR than with SINEMET®. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET® CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Care should be exercised in administering SINEMET® CR to patients with a history of recent myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage administration and titration, in a facility with provisions for intensive cardiac care.

SINEMET® CR should be administered cautiously to patients with a history of peptic ulcer disease or of convulsions.

Precautions: *General:* Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy (see ADVERSE REACTIONS).

Patients with chronic wide angle glaucoma may be treated cautiously with SINEMET® CR (levodopa and carbidopa), provided the intraocular pressure is well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Use in Children: Safety of SINEMET® CR in patients under 18 years of age has not been established.

Use in Pregnancy and Lactation: Although the effects of SINEMET® CR on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see TERATOLOGIC AND REPRODUCTIVE STUDIES in Product Monograph). Therefore, use of SINEMET® CR in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to the mother and to the fetus. SINEMET® CR should not be given to nursing mothers.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET® CR:

Antihypertensive drugs: Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment of patients receiving antihypertensive drugs. Therefore, when therapy with SINEMET® CR is started, dosage adjustment of the antihypertensive drug may be required.

Psychoactive drugs: Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET® CR should be observed carefully for loss of therapeutic response.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations. (For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.)

Other drugs: Although specific interaction studies were not performed with other concomitant drugs, in clinical trials of SINEMET® CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, thiazides, digoxin, H_2 antagonists, salicylates and other nonsteroidal anti-inflammatory drugs. SINEMET® CR was also used with other antiparkinson agents (see DOSAGE and ADMINISTRATION).

Adverse Reactions: In controlled clinical trials involving 748 patients with moderate to severe motor fluctuations, SINEMET® CR (levodopa and carbidopa) did not produce side effects which were unique to the controlled-release formulation.

The adverse reaction reported most frequently was dyskinesia (12.8%). Occasionally, prolonged, and at times, severe afternoon dyskinesias have occurred in some patients.

Other adverse reactions that were reported frequently were: nausea (5.5%), hallucinations (5.3%), confusion (4.9%), dizziness (3.5%), headache (2.5%), depression (2.5%), chorea (2.5%), dry mouth (2.3%), somnolence (2.1%), dream abnormalities (2.1%), dystonia (2.0%) and asthenia (2.0%).

Adverse reactions occurring less frequently (less than 2%) were:

System/%: *Body as a whole:* Chest pain 1.7%, Fatigue 0.9%, Weight loss 0.8%.
Cardiovascular: Orthostatic hypotension 0.8%, Palpitation 0.8%, Hypotension 0.5%.
Nervous System / Psychiatric: Insomnia 1.7%, Falling 1.6%, On-off phenomenon 1.2%, Paresthesia 0.9%, Disorientation 0.8%, Anxiety disorders 0.8%, Decreased mental acuity 0.7%, Extrapyramidal disorder 0.7%, Gait abnormalities 0.7%, Agitation 0.5%, Memory impairment 0.5%.
Gastrointestinal: Anorexia 1.9%, Constipation 1.5%, Vomiting 1.3%, Diarrhea 1.2%, Gastrointestinal pain 0.9%, Dyspepsia 0.8%.
Musculoskeletal: Muscle cramps 0.9%.
Respiratory: Dyspnea 1.6%.
Special Senses: Blurred vision 1.1%.

Other adverse reactions that have been reported with levodopa or SINEMET® and may be potential side effects with SINEMET® CR are listed below:

Nervous System: Ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome.
Psychiatric: Sleepiness, euphoria, paranoid ideation and psychotic episodes, and dementia.
Cardiovascular: Arrhythmias, non-specific ECG changes, flushing, phlebitis.
Gastrointestinal: Bitter taste, sialorrhea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.
Integumentary: Increased sweating, dark sweat, rash, hair loss.
Genitourinary: Urinary frequency, retention, incontinence, hematuria, dark urine, nocturia and priapism.
Special Senses: Diplopia, dilated pupils, oculogyric crises.
Hematologic: Leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.
Miscellaneous: Weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, hypertension, neuroleptic malignant syndrome, malignant melanoma (see CONTRAINDICATIONS).

Convulsions have occurred; however, a causal relationship with levodopa or levodopa/carbidopa combinations has not been established.

Dosage and Administration: SINEMET® CR (levodopa and carbidopa) Tablets contain a 4:1 ratio of levodopa to carbidopa. SINEMET® CR 200/50 contains levodopa 200 mg/carbidopa 50 mg per tablet. SINEMET® CR 100/25 contains levodopa 100 mg/carbidopa 25 mg per tablet. The daily dosage of SINEMET® CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

SINEMET® CR 200/50 may be administered as whole or as half tablets. SINEMET® CR 100/25 should only be administered as whole tablets. To maintain the controlled-release properties of the product, tablets should not be chewed or crushed.

Standard antiparkinson drugs, other than levodopa alone, may be continued while SINEMET® CR is being administered, although their dosage may have to be adjusted. The delayed onset of action with SINEMET® CR may require the supplemental use of conventional SINEMET® Tablets for optimal control in the mornings.

Initial Dosage and Titration for Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations: Dosage with SINEMET® CR 200/50 should be substituted at an amount that eventually provides approximately 10 to 30 percent more levodopa per day. The interval between doses should be prolonged by 30 to 50 percent. Initially, patients should receive SINEMET® CR 200/50 at a dosage that provides the same amount of levodopa, but with a longer dosing interval. Depending on clinical response, the dosage may be increased.

A guide for the initiation of treatment with SINEMET® CR 200/50 is shown in the following table:

Guideline for Initial Conversion from SINEMET® to SINEMET® CR 200/50

SINEMET® Total Daily Dose Levodopa (mg)*	*SINEMET® CR 200/50 (levodopa 200 mg/ carbidopa 50 mg) Suggested Dosage Regimen*
300-400	1 tablet b.i.d.
500-600	1 1/2 tablets b.i.d. or 1 tablet t.i.d.
700-800	A total of 4 tablets in 3 or more divided doses (e.g., 1 1/2 tablets a.m., 1 1/2 tablets early p.m., and 1 tablet later p.m.)
900-1000	A total of 5 tablets in 3 or more divided doses (e.g., 2 tablets a.m., 2 tablets early p.m., and 1 tablet later p.m.)

*For dosing ranges not shown in the table, see DOSAGE AND ADMINISTRATION.

SINEMET® CR 100/25 is available to facilitate titration when 100 mg steps are required and as an alternative to the half tablet of SINEMET® CR 200/50.

Initial Dosage for Patients Currently Treated with Levodopa Alone: Levodopa must be discontinued at least eight hours before therapy with SINEMET® CR 200/50 is started. SINEMET® CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET® CR 200/50 two times daily.

Patients Without Prior Levodopa Therapy: Experience with SINEMET® CR is limited in the *de novo* parkinsonian patients.

SINEMET® CR 100/25 may be used in early stage patients who have not had prior levodopa therapy or to facilitate titration when necessary in patients receiving SINEMET® CR 200/50. The initial recommended dose is 1 tablet of SINEMET® CR 100/25 twice daily. For patients who require more levodopa, a daily dose of 1 to 4 tablets of SINEMET® CR 100/25 twice a day is generally well-tolerated.

When appropriate, levodopa therapy may also be initiated with SINEMET® CR 200/50. The initial recommended dose in patients with mild to moderate disease is 1 tablet of SINEMET® CR 200/50 two times daily. Initial dosages should not exceed 600 mg per day of levodopa or be given at intervals of less than 6 hours.

Titration: Doses and dosing intervals must be adjusted on an individual basis, depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended. Most patients have been adequately treated with 2 to 8 tablets of SINEMET® CR 200/50 per day, administered as divided doses at intervals ranging from 4 to 12 hours during the waking day.

If the divided doses of SINEMET® CR 200/50 are not equal, it is recommended that the smaller doses be given at the end of the day.

Maintenance: Because Parkinson's disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of SINEMET® CR may be required.

Addition of Other Antiparkinson Medications: Anticholinergic agents, dopamine agonists, amantadine and lower doses of selective MAO-B inhibitors can be given with SINEMET® CR. When combining therapies, dosage adjustments may be necessary.

Interruption of Therapy: Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET® CR is required, especially if the patient is receiving neuroleptics (see PRECAUTIONS).

If general anesthesia is required, SINEMET® CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

Availability of Dosage Form: No. 2042 - SINEMET® CR 100/25 is a pink-colored, oval-shaped, biconvex, compressed tablet, engraved SINEMET CR on one side and 601 on the other. Available in bottles of 100.

No. 2041 - SINEMET® CR is peach-colored, oval-shaped, biconvex, scored compressed tablet, engraved SINEMET CR on one side and 521/521 on the other. Available in bottles of 100.

Product Monograph Available on Request

(384-a,4,93) 04-94-SCR-93-CDN-0040-JA

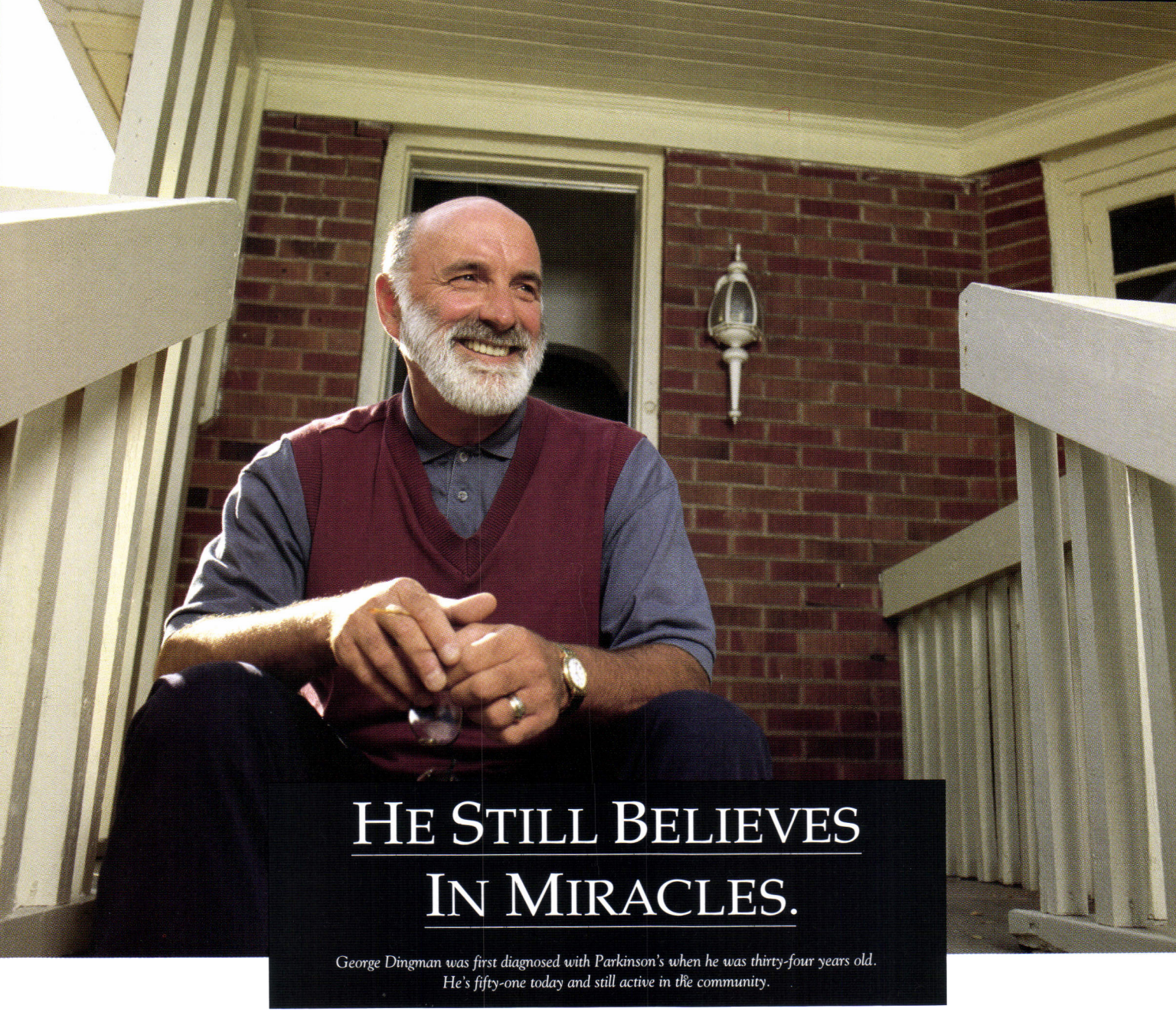
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He still believes in the unlikely and even the impossible. That's just the way he is – even if it does sound naïve. He just thinks it's healthier to look for possibilities than to accept the way things are. Maybe miracles are too much to expect. But perhaps having a better life with Parkinson's doesn't take a miracle. There's evidence now to suggest that maintaining consistent drug levels can improve the control of Parkinson's – particularly as the disease progresses. It's not exactly a miracle. But, to someone like George, it means hope.

Pr SINEMET® CR 200/50 100/25
(levodopa/carbidopa) CONTROLLED-RELEASE

TREAT TODAY WITH TOMORROW IN MIND

Other patients' experience may differ.
Before prescribing, please consult the attached prescribing information. ®Trademark of Merck & Co., Inc./Merck Frosst Canada Inc., and DuPont Merck Pharma, R.U. PAAB

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1995 Canadian Electroencephalography Examination

Organized by the Canadian Society of Clinical Neurophysiologists

To assure and maintain a high standard of competence in clinical electroencephalography across Canada, the Canadian Society of Clinical Neurophysiologists (CSCN) conducts an annual examination in EEG and related subjects for those eligible physicians entering EEG practice who elect to take it. Successful candidates will be given a certificate by the CSCN. The Provincial Licensing Bodies and the Royal College of Physicians and Surgeons of Canada have been informed of this examination and of the objective of the CSCN to maintain high standards in the practise of Clinical Neurophysiology in Canada.

Deadline with application: May 1, 1995

Eligibility:	Candidates shall have an M.D. degree from a medical school approved by the CSCN and at least six months of EEG training.	
Format:	*Written Examination*	Friday, June 23, 1995, Victoria, B.C. 3-hour, 100 question multiple choice
	Oral Examination	Saturday, June 24, 1995, Victoria, B.C.
Language:	The written and oral will be offered in both English and French	
Application:	Please apply by letter to:	Dr. Warren T. Blume CSCN, Examining Committee University Hospital, EEG Dept. 339 Windermere Road London, Ontario N6A 5A5

Examens d'EEG de la SCNC pour 1995

Organisé par la société canadienne de neurophysiologie clinique

Afin d'assurer le maintien d'un haut niveau de compétence en électroencéphalographie clinique au Canada, la Société canadienne de neurophysiologie clinique (SCNC) organise chaque année un examen en EEG et ses sujets connexes auquel peuvent se présenter les médecins admissibles qui se lancent dans la pratique de l'EEG. Les heureux candidats recevront un certificat de la SCNC. Les organismes provinciaux de réglementation professionelle et le Collège royal des médecins et chirurgiens du Canada ont été informés de cet examen, ainsi que de l'objectif de la SCNC de maintenir des normes élevées dans la pratique de la neurophysiologie clinique au Canada.

Date limite de soumission des candidatures accompagnées des frais d'examen : 1er mai

Admissibilité :	Un doctorat en médecine d'une faculté de médecine approuvée par la SCNC, et au moins six mois de formation en EEG	
Format :	*Examen écrit*	Le vendredi 23 juin 1995, Victoria (C.-B.) Trois heures, 100 questions à choix multiples.
	Examen oral	le samedi 24 juin 1995, Victoria (C.-B.)
Langue :	Les examens écrits et oraux seront offerts en anglais et en français.	
Candidature :	Veuillez soumettre votre candidature par écrit à :	Dr. Warren T. Blume CSCN, Examining Committee University Hospital, EEG Dept. 339 Windermere Road London, Ontario N6A 5A5

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MAINTENANT SUR LA LISTE DE MÉDICAMENTS DU QUÉBEC

Pr **NEURONTIN***

capsules de gabapentine

dosées à 100 mg, 300 mg, 400 mg

POUR UNE MAÎTRISE SUPPLÉMENTAIRE DES CRISES D'ÉPILEPSIE...



... ET AVOIR LA SITUATION BIEN EN MAIN!

Neurontin est maintenant offert au Canada comme traitement adjuvant des crises partielles et tonico-cloniques secondairement généralisées.

Contrairement à ce qui se passe avec les autres traitements adjuvants, il n'y a pas d'interaction pharmacocinétique entre Neurontin et les anticonvulsivants d'usage courant[+1].

Maintenant, avec Neurontin, la décision d'utiliser des traitements en association pour obtenir une maîtrise supplémentaire des crises est facile à prendre.

*carbamazépine, phénobarbital, phénytoïne, acide valproïque [1]Monographie de Neurontin (gabapentine)

PARKE-DAVIS Scarborough, Ontario, M1L 2N3 * M. de comm. Warner-Lambert Company, Parke-Davis Division, Warner-Lambert Canada Inc. usager aut.

ACIM PAAB CCPP

Pour documentation voir pages xviii, xvix.

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On peut facilement reconnaître le jeune patient épileptique traité au Tegretol® CR.

Excellent contrôle des crises

P Tegretol® CR (carbamazépine à libération contrôlée) maîtrise les crises chez de nombreux patients, causant peu d'impact sur la fonction cognitive[1,2]. Tegretol CR permet à de nombreux patients de penser clairement et de donner le meilleur d'eux-mêmes[1,2].

Taux sanguins uniformes

Tegretol CR cause moins de «hauts et de bas» dans les taux sanguins que le Tegretol conventionnel. Les effets secondaires sont ainsi réduits et le modèle de fonction cognitive est plus stable[3,4].

Posologie b.i.d. commode

Lorsque vous instituez ou remplacez un traitement, pensez au Tegretol CR. Il est présenté en comprimés à 200 mg et 400 mg facilement divisibles pour une plus grande souplesse d'administration et améliorer l'observance du patient.



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Aide les épileptiques à réaliser leur plein potentiel.

PAAB CCPP MEMBRE ACIM G-93095F

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