The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques

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The Official Journal of

The Canadian Neurological Society
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association of Child Neurology

Volume 20, No. 3 **August 1993**

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The Canadian Journal of Neurological Sciences

VOLUME 20, NO. 3, AUGUST 1993

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Table of Contents

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Le Journal Canadien des Sciences Neurologiques

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Pour documentation voir page xx

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For detailed instructions regarding style and layout, authors should refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained by writing to the Journal office, but the main points are summarized here. Articles should be submitted under conventional headings of "introduction", "methods and materials", "results", "discussion", but other headings and subheadings will be considered if more suitable for a particular manuscript.

A title page should identify the title of the article, authors, name of institution(s) from which the work originated and the address, telephone and fax numbers of the corresponding author. Pages of text should be numbered consecutively. Acknowledgements, including recognition of financial support should be typed on a separate page at the end of the text.

The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

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Review Articles on selected topics are also published by the Journal. They are usually invited, but unsolicited reviews will be considered. It is recommended that authors intending to submit review articles contact the Editor in advance.

Letters to the Editor: Letters concerning matters arising in recent articles are welcome. Letters should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

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Number references in the order of their citation in the text. Those cited only in tables or in legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration. Titles of journals should be abbreviated according to the style used in Index Medicus. References should include the names of up to five authors; if there are more, cite the first three, then "et al.". Provide the full title, year of publication, volume number and inclusive pagination for journal articles. For any reference cited as "in press", five copies of the article must accompany the author's manuscript. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide five copies of "submitted" manuscripts. Avoid "personal communications" and, if necessary, include them in the body of the text, not among the references. Reference citations should not include unpublished presentations or other non-accessible material. Books or chapter references should also include the place of publication and the name of the publisher. Examples of correct forms of reference follow:

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Chapter in a book

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

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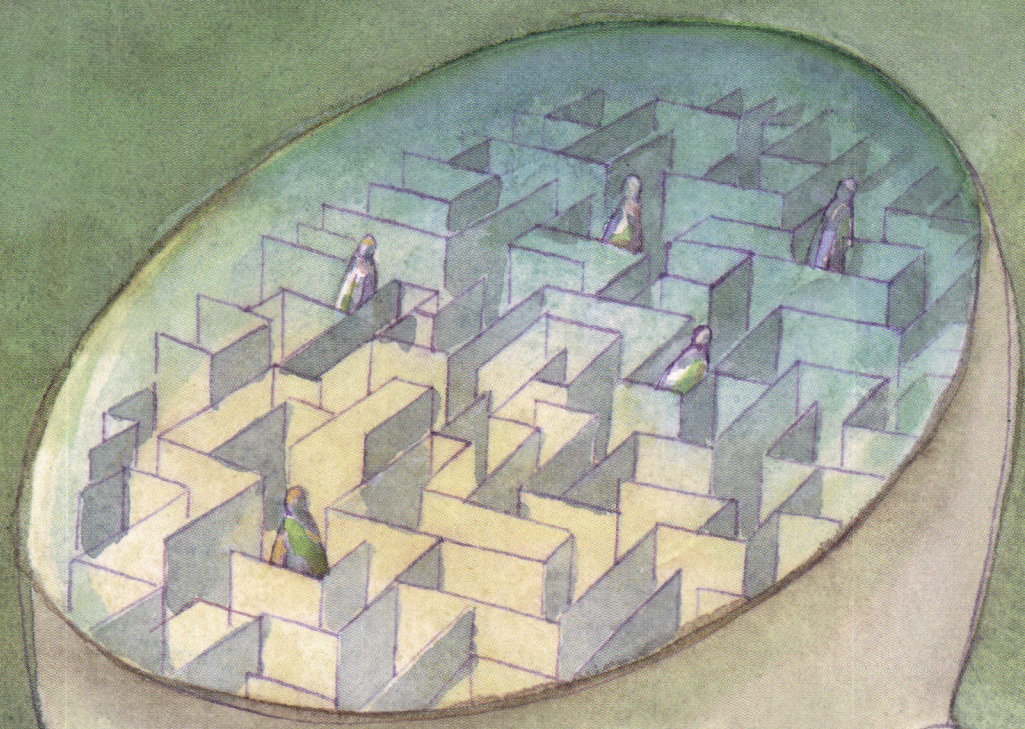
Tables

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

It's about time...



In the 50s, GABA (γ-aminobutyric acid) was identified as an inhibitory neurotransmitter.

In the 60s, GABA-transaminase (GABA-T) was pinpointed as an enzyme involved in GABA breakdown.

Research led to the suspicion that GABA activity impairment may play a role in epilepsy, and that if GABA levels were increased, seizures might decrease. However, the first GABA-related medication was only introduced in the early 70s in North America.

Its mode of action and effect on GABA are unknown.

Specific GABA-T inhibitors have been developed and tested on animals and humans. They reduce GABA-T activity and increase the pre-synaptic GABA pool.

Specific GABA-T inhibition – an important step toward better seizure control.

Pinpointing GABA-T for better seizure control

MARION MERRELL DOW
CANADA

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There's only one thing your TIA patients want from a stroke prevention therapy.

Tomorrow.

What patients at risk want most is the reassurance everything possible is being done to prevent another event.

By making Ticlid a part of your patients' treatment, you can give them that reassurance.

Because for non-cardiogenic thromboembolic stroke – the most common form of the disease[1] – there is no therapy proven more effective than Ticlid.

In two landmark studies, Ticlid has been shown to significantly reduce the risk of both initial and recurrent stroke.[2,3]

During the critical first year after a TIA, Ticlid reduced the incidence of stroke by nearly half relative to ASA. And its superiority was maintained over a 5 year term, in women as well as men.[2,4]

Ticlid also performed significantly better than placebo in recurrent stroke, and remains the only therapy indicated for the prevention of initial and recurrent stroke in both men and women.[3,5]

With Ticlid, side effects have been shown to be manageable, transient and to occur early in therapy, with most common side effects being relieved by a temporary dose reduction.[2,6]

In clinical trials, there was a 2.4% incidence of neutropenia (0.8% severe). Upon immediate discontinuation of therapy, the neutrophil count usually returned to normal within one to three weeks.[2,3]

To manage the condition requires regular WBC monitoring every two weeks for the first three months of therapy.[6]

Ticlid. After you tell your patients about the risk of stroke, tell them about Ticlid.

And let them get on with their lives.

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TICLID (ticlopidine hydrochloride) 250 mg Tablets
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).
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 x 10^9 cells/L). The incidence of severe neutropenia (ANC<0.45 x 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 is reversible, and recovery usually occurs within 1-3 weeks after discontinuation of the drug.
In clinical trials, thrombocytopenia (defined as a platelet count of <0.8 x 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 count and platelet count performed every 2 weeks during the first 3 months of therapy. The incidence of neutropenia or thrombocytopenia after three months of therapy is not appreciably higher than the background levels observed in control groups, and continued periodic monitoring is not warranted. However, for the duration of ticlopidine therapy, any signs or symptoms suggestive of neutropenia or thrombocytopenia should be promptly investigated with complete blood counts and platelet counts.
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 43μmol/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
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 WBC count with differential and platelet count performed* every 2 weeks during the first 3 months of therapy. 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.
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.
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 t1/2 of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted *when starting or stopping concomitant therapy with ticlopidine hydrochloride.*
Theophylline	t1/2 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, thromobcytopenic 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, microcrystalline 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 2-week Patient Starter Packs 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.
REFERENCES 1. Adapted from Feinberg W. Antithrombotic therapy in stroke and transient ischemic attacks. *American Family Physician* 1989;40(Suppl):53S-9S. 2. Hass WK et al. Ticlopidine Aspirin Stroke Study (TASS). A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Eng J Med* 1989;321;501-7. 3. Gent M at al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *The Loncet* 1989 Jun:1215-20. 4. Ticlopidine Aspirin Stroke Study (TASS). Data on file, Syntex Inc.,Vol.52,Oct 1989. 5. Compendium of Pharmaceuticals and Specialties, 1992. 6. Ticlid product monograph.

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Hope for better seizure control

GABA-T is an enzyme which breaks down GABA, a neurotransmitter that inhibits paroxysmal discharges in the brain.

Although a number of antiepileptic drugs act on the GABA system, none of the available anticonvulsants are known to exert specific GABA-T inhibition.

Research into GABA-T inhibition is helping develop specific medications which may help more epileptic patients achieve better seizure control.

Pinpointing GABA-T for better seizure control

MARION MERRELL DOW
CANADA

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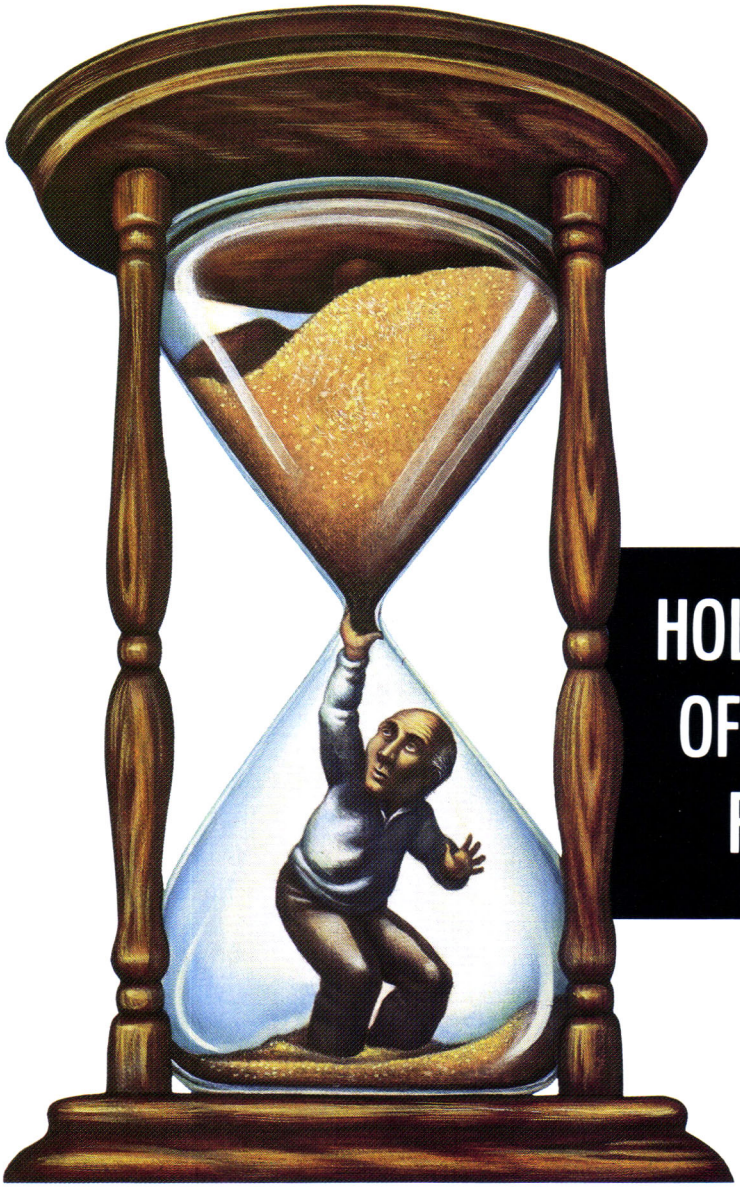

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For brief prescribing information see page xxi

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

Excellent contrôle des crises

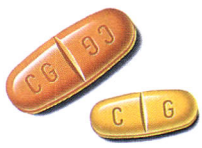
℗ Tegretol® CR (carbamazépine à libération contrôlée) maîtrise les crises chez de nombreux patients, causant peu d'impact sur la fonction cognitive[1,2]. Tegretol CR permet à de nombreux patients de penser clairement et de donner le meilleur d'eux-mêmes[1,2].

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.



TEGRETOL® CR.

Aide les épileptiques à réaliser leur plein potentiel.

PAAB CCPP MEMBRE ACIM G-93095F

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Pour documentation voir pages xvii, xviii

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For brief prescribing information see page xix