The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques

29th Canadian Congress of Neurological Sciences
June 27 - 30, 1994
St. John's, Newfoundland

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. 4 November 1993

https://doi.org/10.1017/S0317167100048149 Published online by Cambridge University Press

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VOLUME 20, NO. 4, NOVEMBER 1993

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 Mailed under Publications Mail registration number 3307. Postage paid at Calgary, Alberta. This journal is indexed by *Index Medicus, Excerpta Medica and Current Contents — Clinical Practice and Life Sciences.*

Le Journal Canadien des Sciences Neurologiques est publié trimestriellement. L'abonnement annuel est de 60 $ pour les membres; 70 $ pour les non-membres au Canada; 80 $ pour les Etats Unis et ailleurs. Internes, résidents, fellows pré et post doctoral: 30 $ par année (membres); 40 $ par année (non-membres). Copie simple: 18 $ plus affranchissement et manutention. Toutes les communications et les manuscrits doivent être adressés à Journal Canadien des Sciences Neurologiques, P.O. Box 4220, Station C, Calgary, AB Canada T2T 5N1. Par courrier: 8th Floor, 906 - 12th Avenue S.W., Calgary, AB Canada T2R 1K7. Téléphone (403) 229-9575.
 Posté sous permis de poste-publications no 3307. Port payé à Calgary, Alberta. Le Journal est cité et indexé dans *Index Medicus, Excerpta Medica et Current Contents — Clinical Practice et Life Sciences.*

Advertising representative/Représentant de publicité Sally Gregg, Canadian Journal of Neurological Sciences
810, 906 - 12 Ave. S.W., Calgary, AB Canada T2R 1K7 — (403)-229-9575

Printer/Imprimeur McAra Printing Limited, 105, 2507 - 12th Street N.E., Calgary, Alberta T2E 7L5

ISSN 0317 - 1671

https://doi.org/10.1017/S0317167100048149 Published online by Cambridge University Press

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https://doi.org/10.1017/S0317167100048149 Published online by Cambridge University Press

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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.

References

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:

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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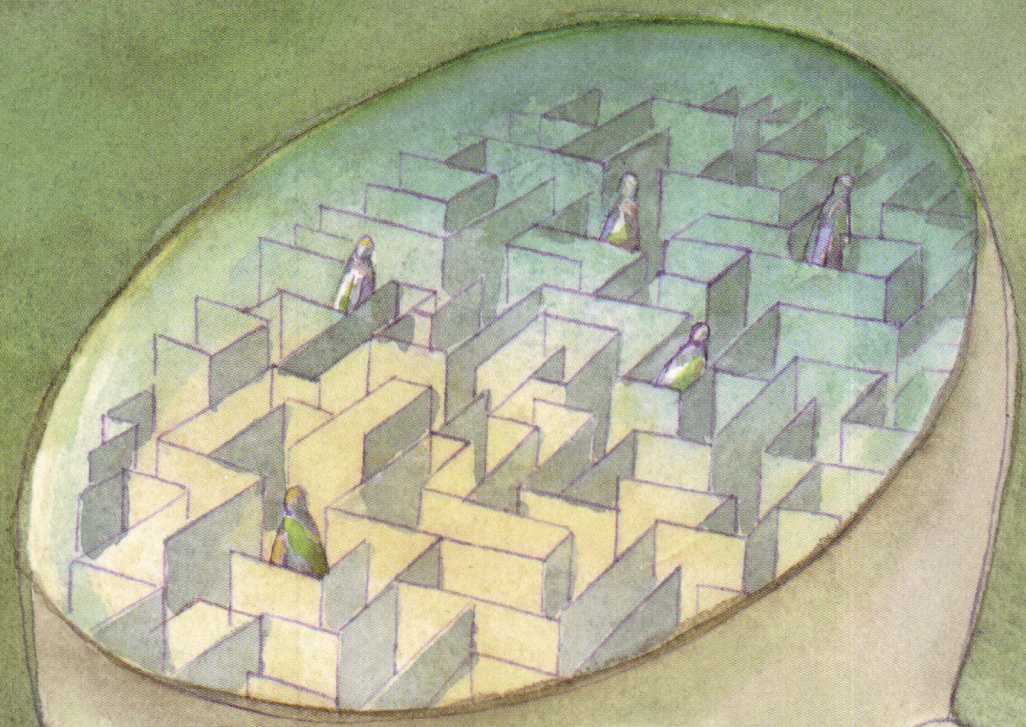
Tables

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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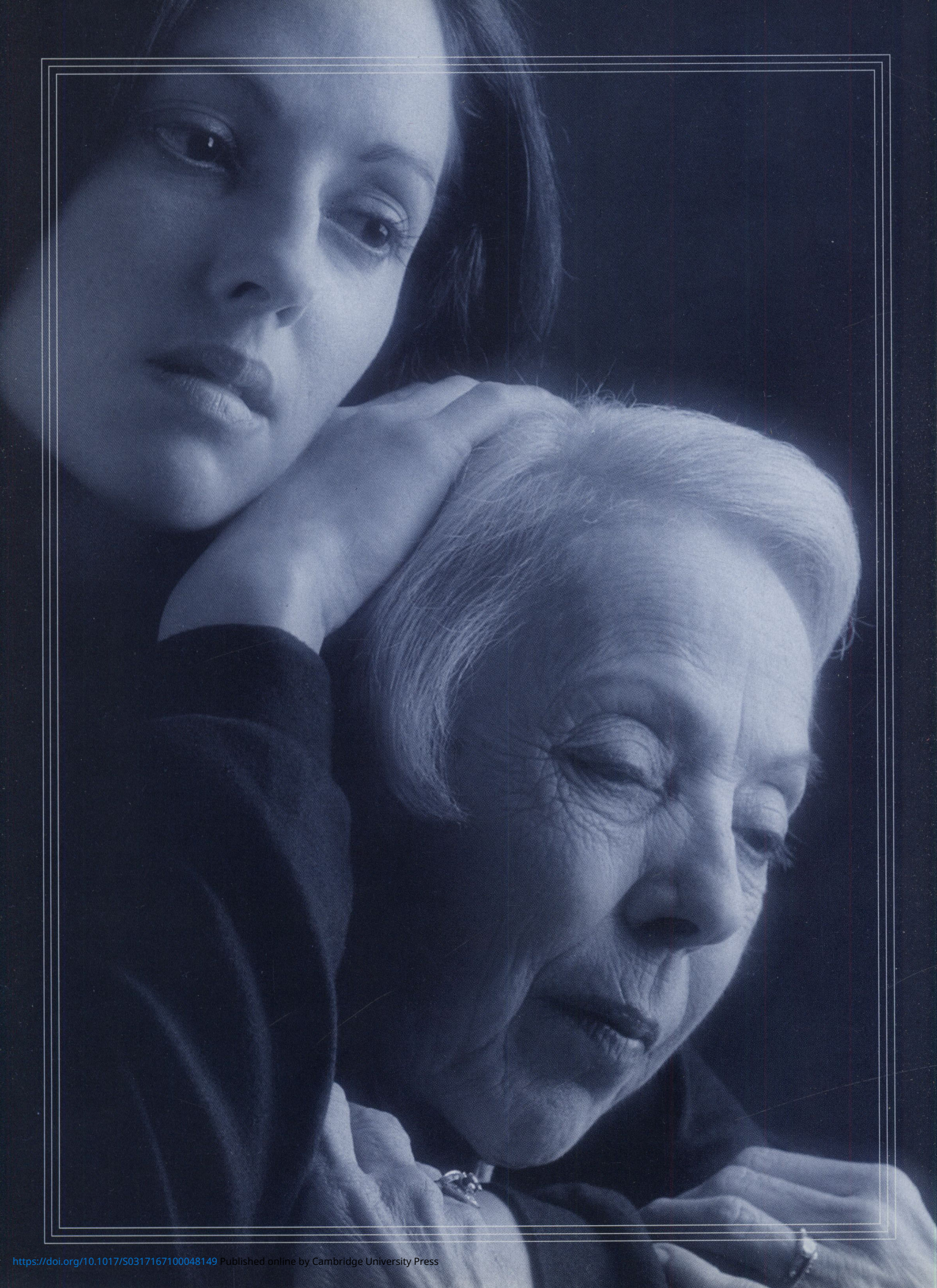

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You may have only days to prevent her stroke.

Which therapy do you choose?

In the prevention of stroke, early intervention is crucial. The risk of initial stroke is greatest in the year following a TIA, with the highest incidence occurring in the first month.[1] And the risk of recurrent stroke increases fivefold after a first stroke.[2]

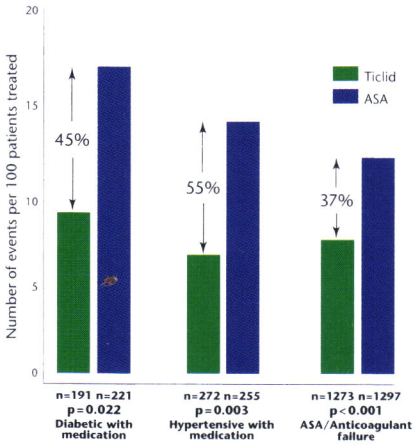
In major clinical trials, Ticlid has been shown to be the most effective therapy for the prevention of non-cardiogenic thromboembolic stroke.[3,4] In the first year after a TIA, Ticlid reduced the risk of stroke 47.6% more than ASA,[5] and particularly benefited certain patient sub-groups.[6,7]

Ticlid has also been proven to reduce the risk of recurrent stroke by almost half compared to ASA.*[8]

To date, Ticlid remains the only therapy indicated for and proven effective in the prevention of both initial and recurrent stroke in men and women.[9,10]

Side effects with Ticlid have been shown to be manageable,

EFFICACY AND RISK REDUCTION IN PATIENT SUB-GROUPS[6,7]



Baseline characteristics of patients in TASS

transient and to occur early in therapy.[10]

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.[10] Managing the condition requires WBC monitoring every two weeks for the first three months of treatment.[10]

From the moment your TIA or stroke patient is at risk, consider Ticlid.

Dosage: 250 mg BID with meals

*Ticlopidine Aspirin Stroke Study, subgroup of patients with completed minor stroke.

Ticlid®

ticlopidine hydrochloride 250 mg tablets

Nothing protects patients from stroke more effectively.

PAAB CCPP MEMBER PMAC

SYNTEX®

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Ticlid®

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 1.2×10^9 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 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 $<0.8 \times 10^{11}$ 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 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**. Easton JD et al. Diagnosis and management of ischemic stroke, *Current Problems in Cardiology*, Vol.7 (5): 1-76, 1983. **2**. Teasell RW. Long-term sequalae of stroke. *Can Fam Physician* 1992;38:381-388. **3**. 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 Engl J Med* 1989;321:501-7. **4**. Gent M et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *The Lancet* 1989 Jun:1215-20. **5**. Biller J, Love B. Recent therapeutic options for stroke prevention. *Hospital Physician* 1991; Vol 27 (6): 13-24. **6**. Grotta JC et al. Prevention of stroke with ticlopidine: Who benefits most? *Neurology* 1992;42:111-5. **7**. Data on file, Syntex Inc.; Subset analysis of Ticlopidine Aspirin Stroke Study (TASS) 1992. **8**. Harbison JW., Ticlopidine versus aspirin for the prevention of recurrent stroke; analysis of patients with minor stroke from the Ticlopidine Aspirin Stroke Study. *Stroke* 1992; 1723-7. **9**. Aspirin* product monograph. (*Aspirin is a registered trademark of Sterling Drug Ltd.) **10**. Ticlid product monograph.

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PARLODEL* (bromocriptine mesylate)

Because quality of life is the issue

ACTIONS Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivate with D_2 type dopamine receptor agonist activity, and has also D_1 dopamine receptor antagonist properties. The dopaminomimetic activity of bromocriptine in the striatum is considered responsible for the clinical benefits seen in selected patients with Parkinson's disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication. Excessive dopaminomimetic drive may, however, provoke psychotic and other adverse reactions.

The extreme variability in G.I. tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

INDICATIONS† Parkinson's Disease: Parlodel (bromocriptine mesylate) has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylase inhibitor), in the symptomatic management of selected patients with Parkinson's disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and schedule of drug administration. Patients maintained on optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure may benefit from the concomitant use of Parlodel, by decreasing the occurrence and/or severity of these manifestations. Since rapid escalation of bromocriptine doses causes severe adverse reactions, it is recommended to combine a slow increase of Parlodel, usually with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine-treated patients than in patients treated with levodopa. Parlodel is not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's disease.

CONTRAINDICATIONS Other than sensitivity to ergot alkaloids, no absolute contraindications to treatment with Parlodel (bromocriptine mesylate) are known. For procedure during pregnancy see "Use in Pregnancy" under Precautions.

WARNINGS Long-term treatment (6-36 months) with Parlodel in doses of 20 to 100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. Where Parlodel was discontinued, these changes slowly reverted to normal.

PRECAUTIONS Parlodel (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with Parlodel; patients should therefore be cautioned against activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery, until their response has been determined.

Care should be exercised when administering Parlodel concomitantly with phenothiazines or antihypertensive agents. Due to drug interaction at the receptor site, dosage should be adjusted accordingly.

Alcohol should be avoided during treatment with Parlodel. In some patients, the concomitant use of Parlodel and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of Parlodel's possible adverse reactions.

Parlodel should always be taken with food. In cases where severe adverse effects, such as nausea, vomiting, vertigo or headaches are severe or persisting, the therapeutic dosage of Parlodel should be reduced to half of one tablet daily (1.25 mg) and increased gradually to that recommended. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in parkinsonian patients receiving Parlodel (see Drug Interactions).

As with all medication, Parlodel should be kept safely out of the reach of children.

Use in Pregnancy: If the patient wishes to become pregnant, Parlodel (bromocriptine mesylate) should be stopped as soon as possible after conception is suspected. In this event immunological confirmation should be done immediately. When pregnancy is confirmed, Parlodel, like all other drugs, should be discontinued unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus.

In human studies with Parlodel (reviewed by Turkalj, I.), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took Parlodel (bromocriptine mesylate) during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Use in Parkinson's Disease: Use of Parlodel (bromocriptine mesylate), particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with Parlodel.

Parlodel administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of Parlodel may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of Parlodel. Caution should be exercised when administering Parlodel to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering Parlodel, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin may increase bromocriptine plasma levels.

Domperidone, a dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonise the therapeutically relevant prolactin lowering effect of Parlodel. It is possible that the antitumorigenic effect of Parlodel in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension which can, on rare occasions, lead to fainting and "shock-like" syndromes has been reported in sensitive patients. This is most likely to occur during the first few days of Parlodel treatment.

When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy were: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

Less common adverse reactions include anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargia, mottling of skin, nasal stuffiness, nervousness, nightmares, parethesia, skin rash, urinary frequency, urinary incontinence, urinary retention and rarely signs or symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE There have been several reports of acute overdosage with Parlodel (bromocriptine mesylate) in children and adults. No life threatening reactions have occurred. Symptoms reported included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. Management is largely symptomatic; the cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION Parlodel (bromocriptine mesylate) should always be taken with food.

Although Parlodel (bromocriptine mesylate) has been found clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of Parlodel is one half of a 2.5 mg tablet (1.25 mg) at bedtime with food to establish initial tolerance. Thereafter, the recommended dosage is 2.5 mg daily in two divided doses, with meals, (half a 2.5 mg tablet twice daily). The dosage may be increased very gradually, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually not exceed 2.5 mg. Clinical assessments are recommended at two week intervals or less during dosage titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40 mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around 10 mg daily or higher. During initial titration it is recommended that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

AVAILABILITY

TABLETS each containing 2.5 mg bromocriptine, as mesylate, available in bottles of 100.
CAPSULES each containing 5 mg bromocriptine, as mesylate, available in bottles of 100.

†*For information on other approved indications, please consult the Parlodel Product Monograph, available to physicians and pharmacists on request.*

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Epival*

divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

INDICATIONS AND CLINICAL USE Sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal; useful in primary generalized seizures with tonic-clonic manifestations. May also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds) accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS Should not be administered to patients with hepatic disease or significant dysfunction. Contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Hepatic failures resulting in fatalities have occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first six months of treatment with valproic acid. A recent survey study of valproate use in the United States in nearly 400,000 patients between 1978 and 1984, has shown that children under two years of age who received the drug as part of multiple anticonvulsant therapy were at greatest risk (nearly 20-fold increase) of developing fatal hepatotoxicity. These patients typically had other medical conditions such as congenital metabolic disorders, mental retardation or organic brain disease, in addition to severe seizure disorders. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.

If Epival is to be used in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, the drug should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immmediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug. The frequency of adverse effects, particularly elevated liver enzymes, may increase with increasing dose. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of women receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid exposed women having children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida). Animal studies have demonstrated valproic acid induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs and an increased incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased 2-to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anti-epileptics. Some reports indicate a possible similar association with the use of other anti-epileptic drugs, including trimethadione, paramethadione, and valproic acid. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of anti-epileptic medication is in doubt, appropriate consultation is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving Epival (divalproex sodium).

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of valproic acid greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment 1 fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of divalproex sodium and valproic acid on the development of the testes and on sperm production and fertility in humans is unknown.

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia and inhibition of platelet aggregation, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the drug should be discontinued.

Because Epival (divalproex sodium) may interact with other anti-epileptic drugs, periodic serum level determinations of concurrently administered anti-epileptics are recommended during the early part of therapy. (See DRUG INTERACTIONS.) There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Epival (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproic acid; the clinical significance of these is unknown.

Driving and Hazardous Occupations: May produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: May potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin (See PRECAUTIONS - General). It is not known if there is a change in unbound (free) phenytoin serum levels. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

ADVERSE REACTIONS The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other anti-epileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anti-epileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Endocrine: There have been reports of irregular menses and secondary amenorrhea in patients receiving valproic acid.

Abnormal thyroid function tests have been reported (See PRECAUTIONS).

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (See PRECAUTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (eg. SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

Other: Edema of the extremities has been reported.

DOSAGE AND ADMINISTRATION The recommended initial dosage is 15/mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases.

The maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 125 mg, it should be given in a divided regimen (See Table).

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by improving seizure control must be weighed against the increased incidence of adverse effects.

As the dosage is raised, blood levels of phenobarbital or phenytoin may be affected (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. **The tablets should be swallowed without chewing.**

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg supplied in bottles of 100 tablets; peach-coloured tablets of 250 mg and lavender-coloured tablets of 500 mg are supplied in bottles of 100 and 500 tablets.

Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total daily dose (mg)	Dosage (mg) Equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1,000	250	250	500
75-89.9	165-197.9	1,250	500	250	500

Product monograph available on request.

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See page xvi.

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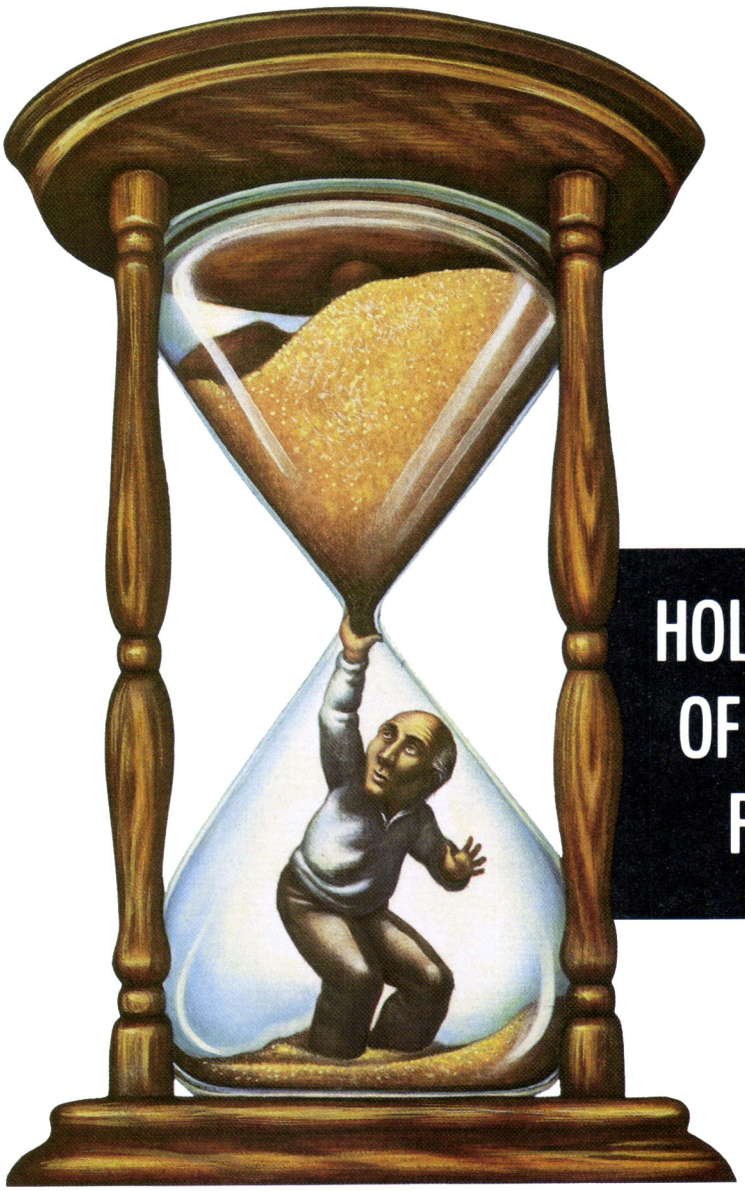
NOW ELDEPRYL IS INDICATED FOR FIRST LINE THERAPY.

Now you can do more than deal with the disability of Parkinson's disease. You can delay it with Eldepryl first line. ☐ In newly diagnosed patients, Eldepryl can significantly retard the worsening of symptoms[2,3] and delay the need for levodopa therapy.[2,4,5] ☐ In fact, Eldepryl can delay the onset of disability and thereby prolong functional life by as much as one year.[1,4] ☐ As well, Eldepryl appears to have a remarkable safety profile. It has been generally well-tolerated with few side effects.[4,6,7] ☐ So when you see patients with Parkinson's disease, prescribe Eldepryl first line. It's their first line of defence against the progression of disability.



HOLD BACK THE DISABILITY OF PARKINSON'S DISEASE FOR AN EXTRA YEAR.[1]

ELDEPRYL® FIRST LINE

selegiline hydrochloride

DELAYS THE PROGRESSION OF DISABILITY.

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For brief prescribing information see page xix.

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

Excellent contrôle des crises

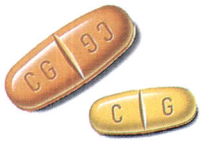
℗ Tegretol® CR (carbamazépine à libération contrôlée) maîtrise les crises chez de nombreux patients, causant peu d'impact sur la fonction cognitive[1,2]. Tegretol CR permet à de nombreux patients de penser clairement et de donner le meilleur d'eux-mêmes[1,2].

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.

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Geigy Dorval, Qué. H9S 1B1

Pour documentation voir pages xvii, xviii

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Good news for patients taking oral contraceptives: Epival does not appear to be associated with O.C. failure.[1]

Epival: For their epilepsy... and their lifestyles

A significant benefit for the newly diagnosed child with absence: Epival not only controls most patients with absence[5], but is also effective against primary generalized seizures with tonic-clonic manifestations.[4,8]

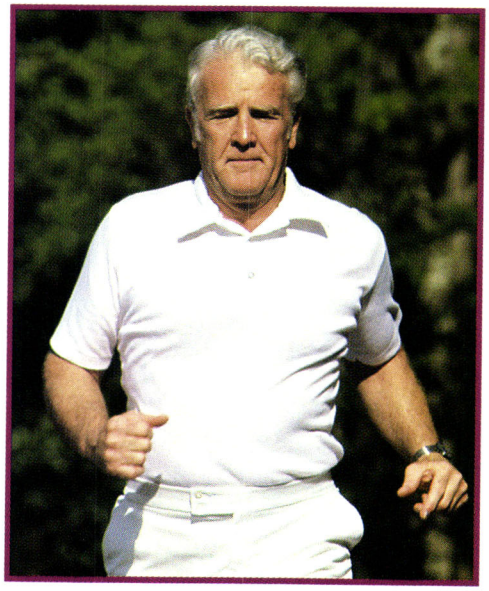
Proven efficacy in a broad range of primary generalized seizures[4,5]

Little effect on learning and cognition[3]

Relatively few clinically substantiated drug interactions[2,9]

Wide therapeutic range[6] for easy titration

Most patients (85%) unable to tolerate other forms of valproic acid were able to take Epival[7]



A dual benefit for the elderly: Epival has relatively few clinically substantiated drug interactions[2,9] and is rarely associated with ataxia or dyskinesias.[3]

Epival* divalproex sodium

A drug of choice in primary generalized seizures

*TM Abbott Laboratories, Limited

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