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La Société Canadienne de Neurologie

The Canadian Neurosurgical Society
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• Submit five high quality copies of the manuscript. Papers will be accepted in English or French. All papers should be accompanied by an abstract of 150 words or less on a separate page, preferably in both languages, although the Journal will provide the translation if required. Manuscripts must be double spaced throughout including references, tables and legends for illustrations. Margins of at least 25mm should be left on all sides.

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• For detailed instructions regarding style and layout 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 will be considered if more suitable. Pages of text should be numbered consecutively.

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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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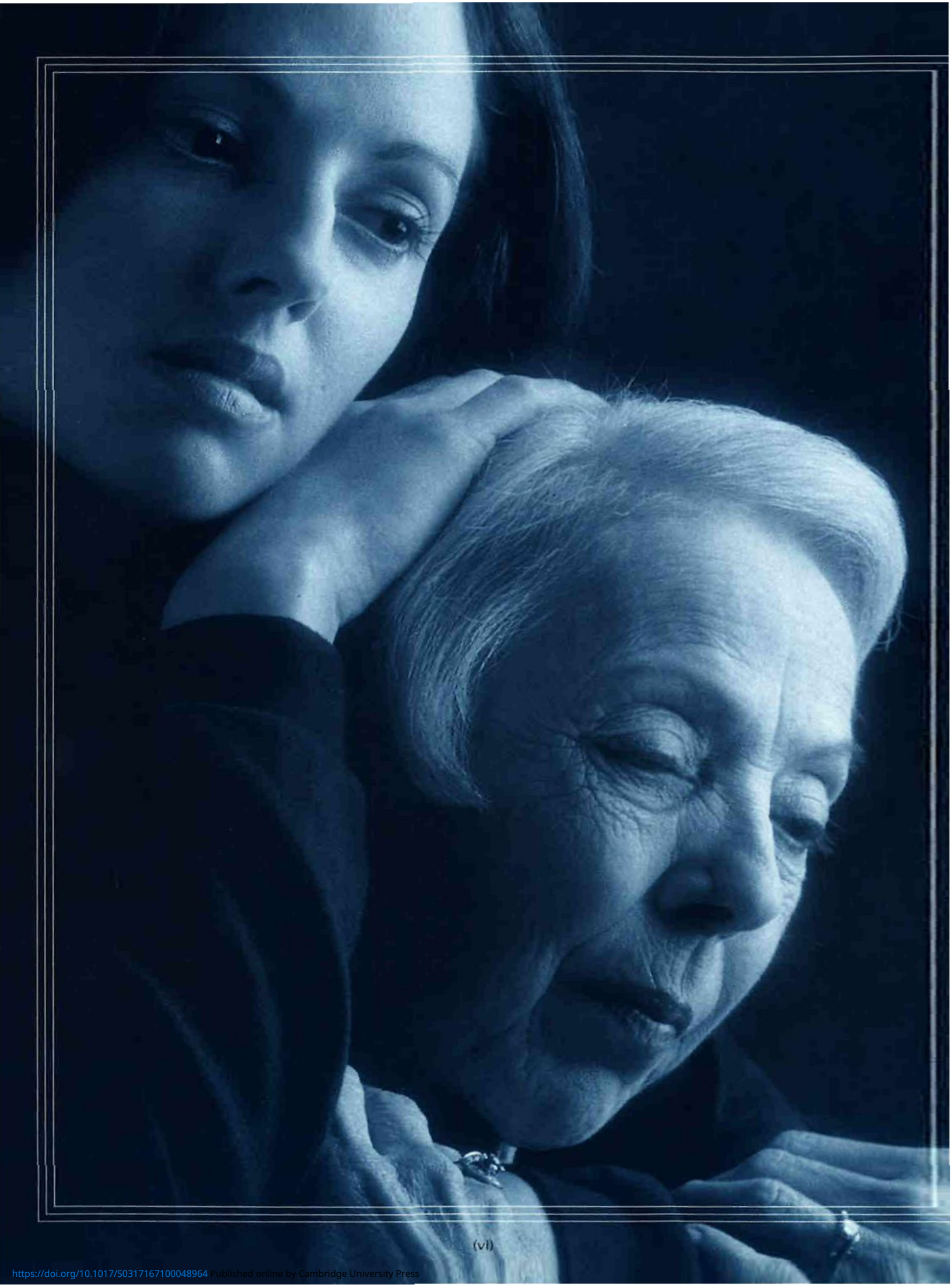

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You may have only days to prevent her stroke.

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]

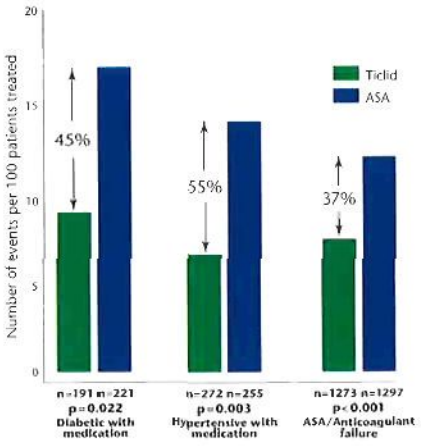
In major clinical trials, Ticlid has been shown to be the most effective therapy for the prevention of non-cardiogenic thromboembolic stroke.[3,4] In the first year after a TIA, Ticlid reduced the risk of stroke 47.6% more than ASA;[5] and particularly benefited certain patient sub-groups.[6,7]

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, transient

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



Baseline characteristics of patients in TASS

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, starting at baseline.[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.

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).

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 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

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 have 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 $<1.2 \times 10^9$ cell/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.

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 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, 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, 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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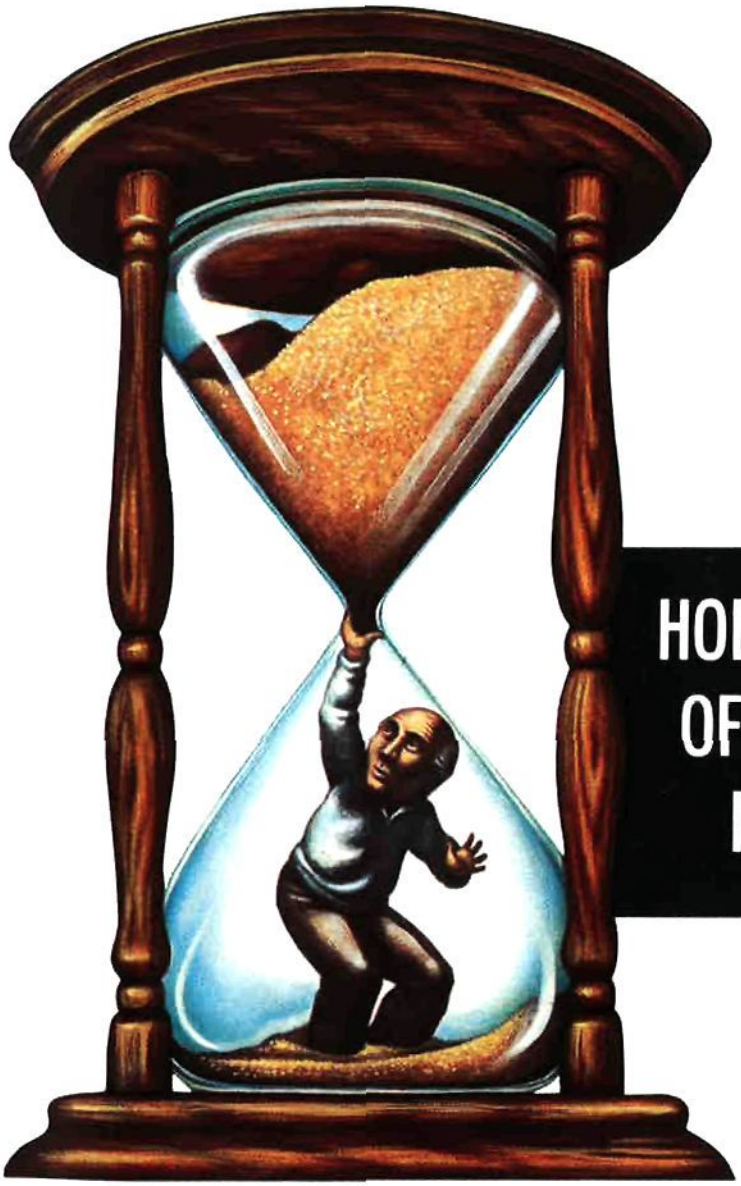

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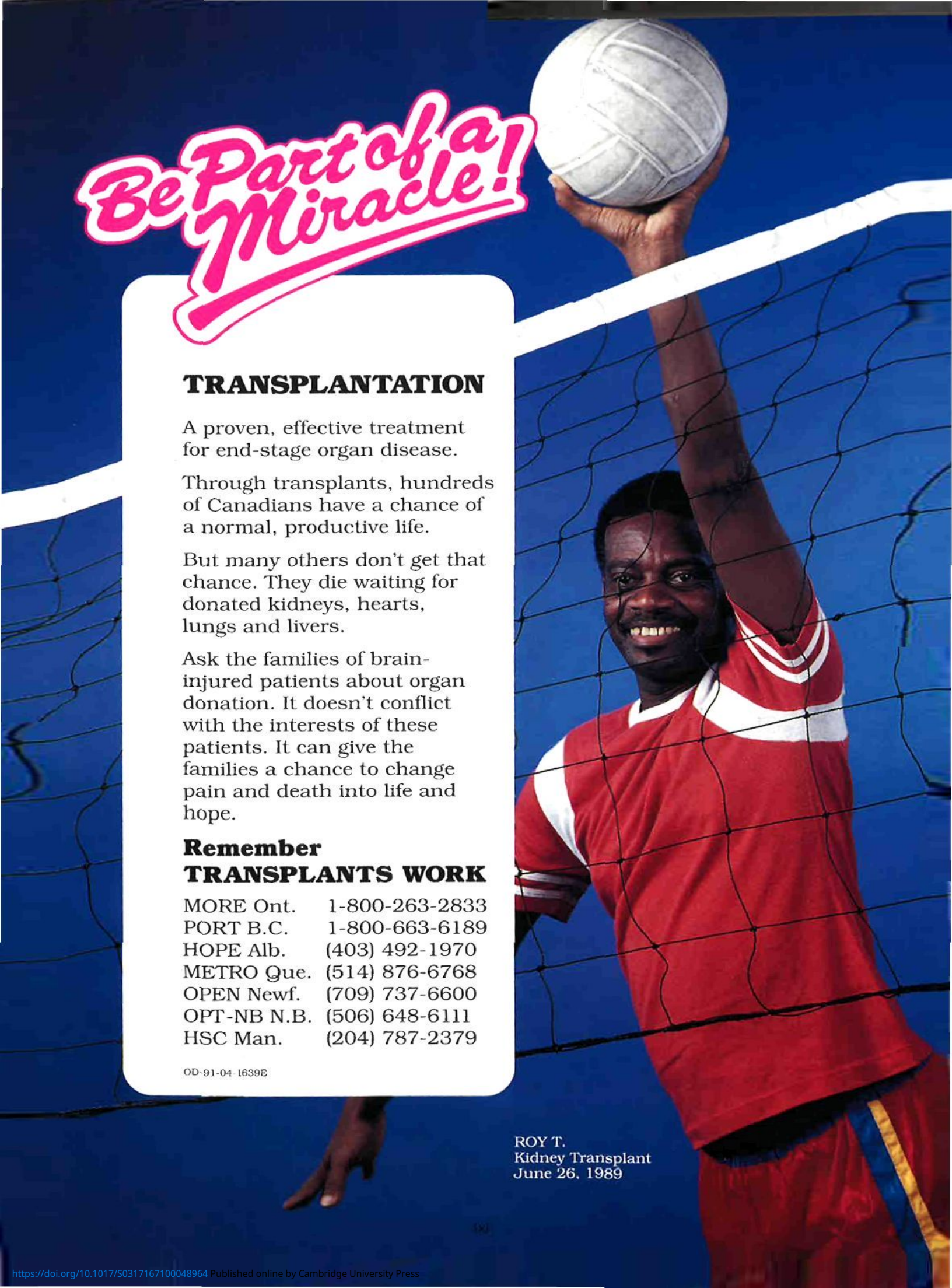

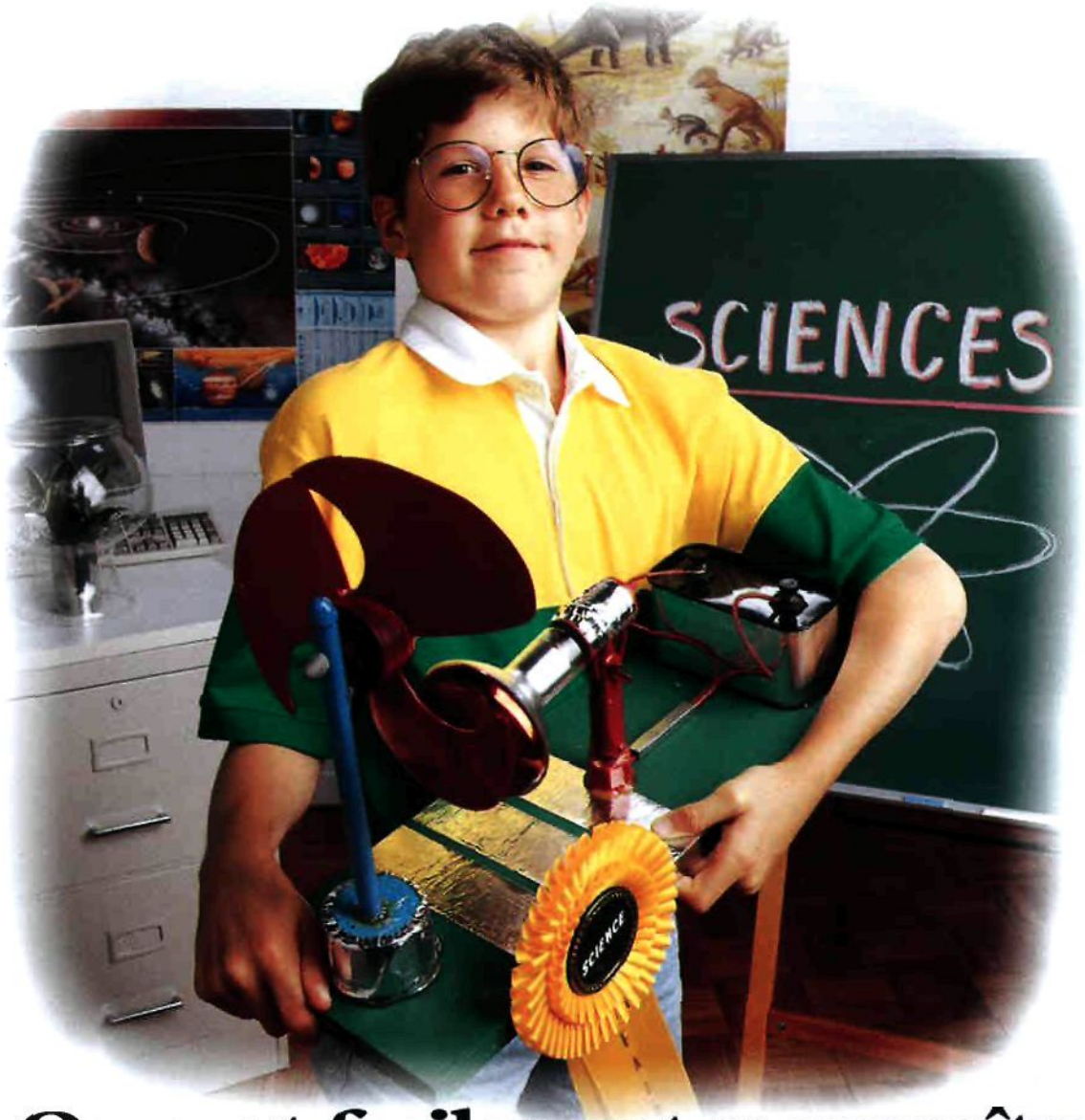

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Epival*

(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.

References: **1.** Dreifuss FE, Langer DH. Side effects of valproate. *Am J Med* 1988;84 (suppl 1A):34-41. **2.** Dean CJ. Valproate. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practices.* Philadelphia, Pa. Lea & Febiger, 1993:chap 77. **3.** Wilder BJ, Ramsay RE, Murphy JV, Karas BJ, Marquardt K, Hammond EJ. Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology* 1983;33:1474-6. **4.** Turnbull DM, Howel D, Rawlins MD, Chadwick DW. Which drug for the adult epileptic patient: phenytoin or valproate? *Br Med J* 1985;290:815-9. **5.** Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. *Epilepsia* 1982;23:693-720. **6.** Kakegawa N, Miyakoshi M, Seino M. Monopharmacy by sodium valproate (SV) and the blood concentration. In: Program and abstracts of the XI Epilepsy International Symposium, September 30, 1979; Firenze, Italy. Abstract. 153. **7.** Epival (divalproex sodium). Product Monograph. Abbott Laboratories, Limited. **8.** Wilder BJ, Rangel RJ. Review of valproate monotherapy in the treatment of generalized tonic-clonic seizures. *Am J Med* 1988;84(suppl 1A):7-13.

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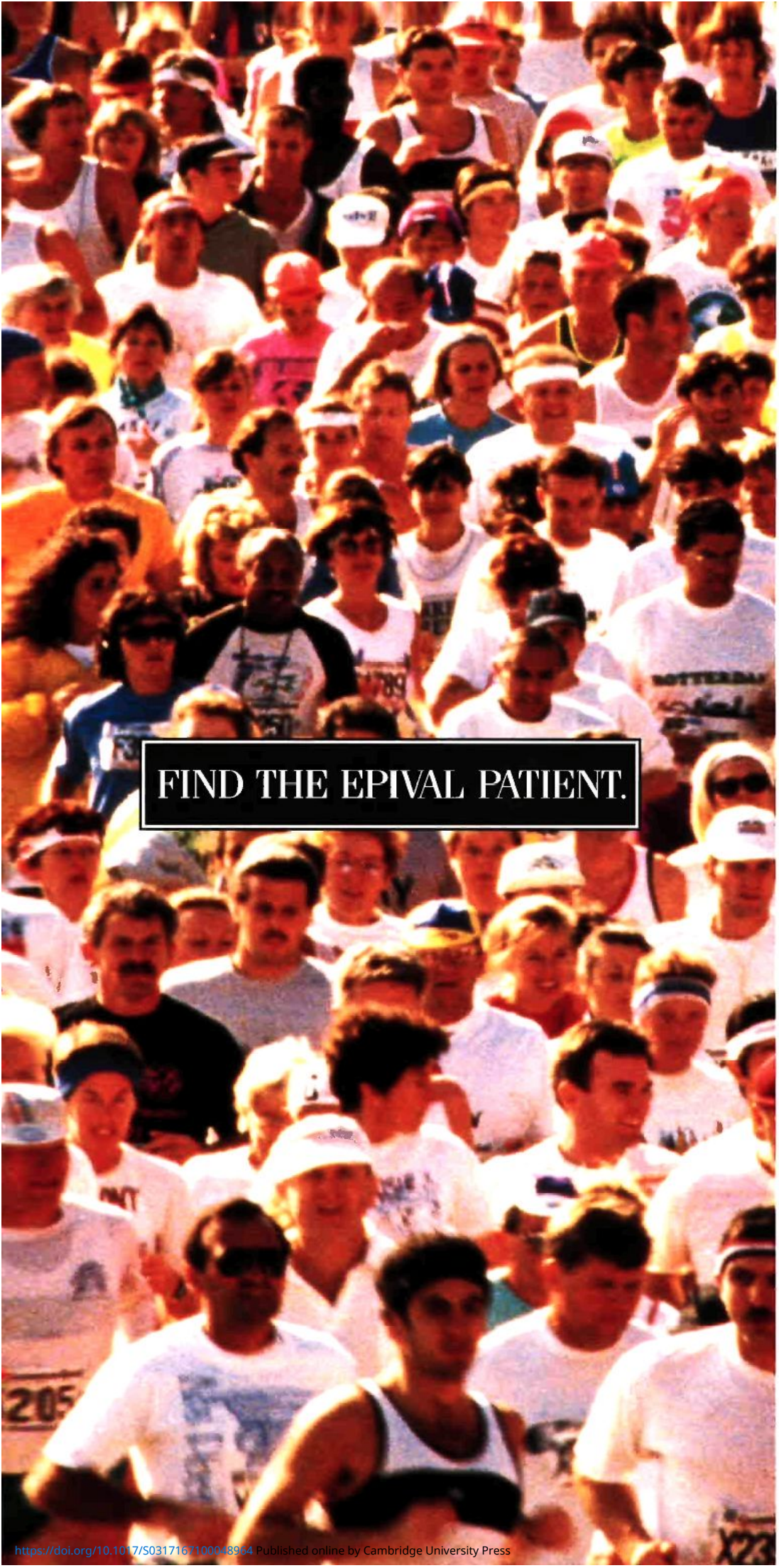

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Epival has been associated with little effect on learning and cognition.[1] It is effective in primary generalized epilepsy[2-4] as well as in partial seizures that secondarily generalize.[5,6†] And it is generally well tolerated,[7] causing less GI irritation (nausea, vomiting and indigestion) than valproic acid.[8]

Prescribe Epival — by name only — to help restore your patients' control over daily living.

Because there's more to anticonvulsant therapy than seizure control.

Write it by name only...

Epival* (divalproex sodium)

Helps put patients back in control.

†For use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal and is useful in primary generalized seizures with tonic-clonic manifestations. EPIVAL may also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

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