

$$\begin{array}{r} 8652 \\ + 9496 \\ \hline 48 \end{array}$$

## Certains antiépileptiques peuvent réprimer plus que les crises.

Il arrive malheureusement que certains antiépileptiques tels la phénytoïne affaiblissent la fonction cognitive.<sup>(1,2,3,4)</sup>

D'autre part, Tegretol® CR (carbamazépine à libération contrôlée) a peu d'impact sur la fonction cognitive tout en procurant un excellent contrôle des crises.<sup>(1,2,3,4)</sup>

Tegretol CR réalise des taux sanguins plus uniformes que le Tegretol conventionnel, ce qui a pour effet de réduire la fréquence des effets secondaires intermittents et de

produire un modèle de fonction cognitive plus stable.<sup>(1,4)</sup>

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Tegretol CR - Parce qu'un antiépileptique ne doit pas affaiblir la capacité d'acquisition.



### TEGRETOL® CR.

*Aide les épileptiques à réaliser leur plein potentiel.*

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**Gelgy**

Mississauga, Ontario  
LSN 2W5

For brief prescribing information see pages xxvii and xxviii (xviii)



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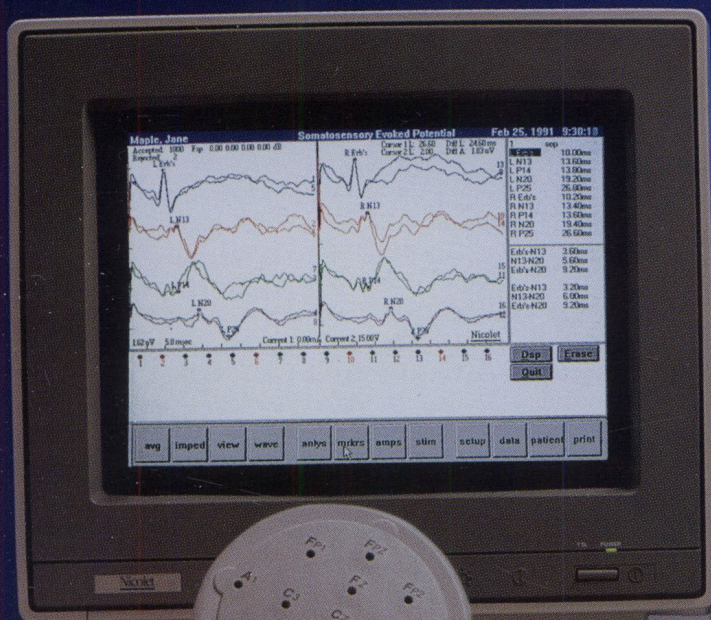
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Through transplants, hundreds of Canadians have a chance of a normal, productive life.

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Now indicated for first line therapy.

Starting Eldepryl with levodopa can further delay disability<sup>1,2,3,4</sup> and prolong functional life.<sup>1,2</sup>

To a parkinsonian patient, a longer functional life is the greatest gift there is. And a combined treatment strategy makes this possible.

By starting Eldepryl with levodopa, you can further extend therapeutic duration<sup>1,3</sup> and improve disability.<sup>1,2</sup>

In fact, in one study, all of the

# HELP PARKINSONIAN PATIENTS HOLD BACK DISABILITY FOR A LONGER TIME.

patients remained totally functional with no major parkinsonian disability at an average disease duration of 6 years.<sup>1</sup>

What's more, several studies have shown that Eldepryl delays the development of disability in Parkinson's disease.<sup>5,6,7</sup>

So when you start Eldepryl with levodopa, you can help your patients spend less time living with disability — and more time living.

**ELDEPRYL**<sup>®</sup>  
selegiline hydrochloride

Delays the disability. May delay the disease.<sup>6,8,9</sup>

PAAB



# Ticlid<sup>®</sup>

**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  $1.2 \times 10^9$  cells/L). The incidence of severe neutropenia (ANC  $< 0.45 \times 10^9$  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, hemorthorax 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 are known concomitantly administered with ticlopidine hydrochloride and the observed interaction if any:

AGENTS	OBSERVED INTERACTION
Acetylsalicylic acid (ASA)	Potential of ASA's effect on collagen-induced platelet aggregation (see WARNINGS).
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in t <sub>1/2</sub> of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride.
Theophylline	t <sub>1/2</sub> 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 were 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**

Event	Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence	Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence
Diarrhea	12.5(6.3)*	5.2(1.8)	4.5(1.7)	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)	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)	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)	1.9(1.4)	1.4(0.9)	0.9(0.4)
Fatulence	1.5(0.1)	1.4(0.3)	0.0(0.0)	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)	1.0(0.4)	0.5(0.4)	0.0(0.0)
Nausea						
Rash						
Neutropenia						
Vomiting						
Pruritus						
Anorexia						

\* 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, hematoma, 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.

**DOSE 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.

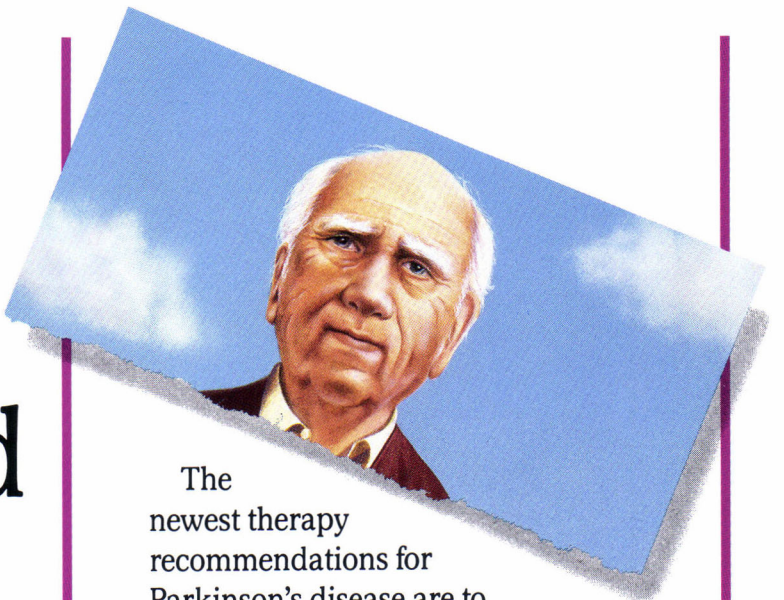
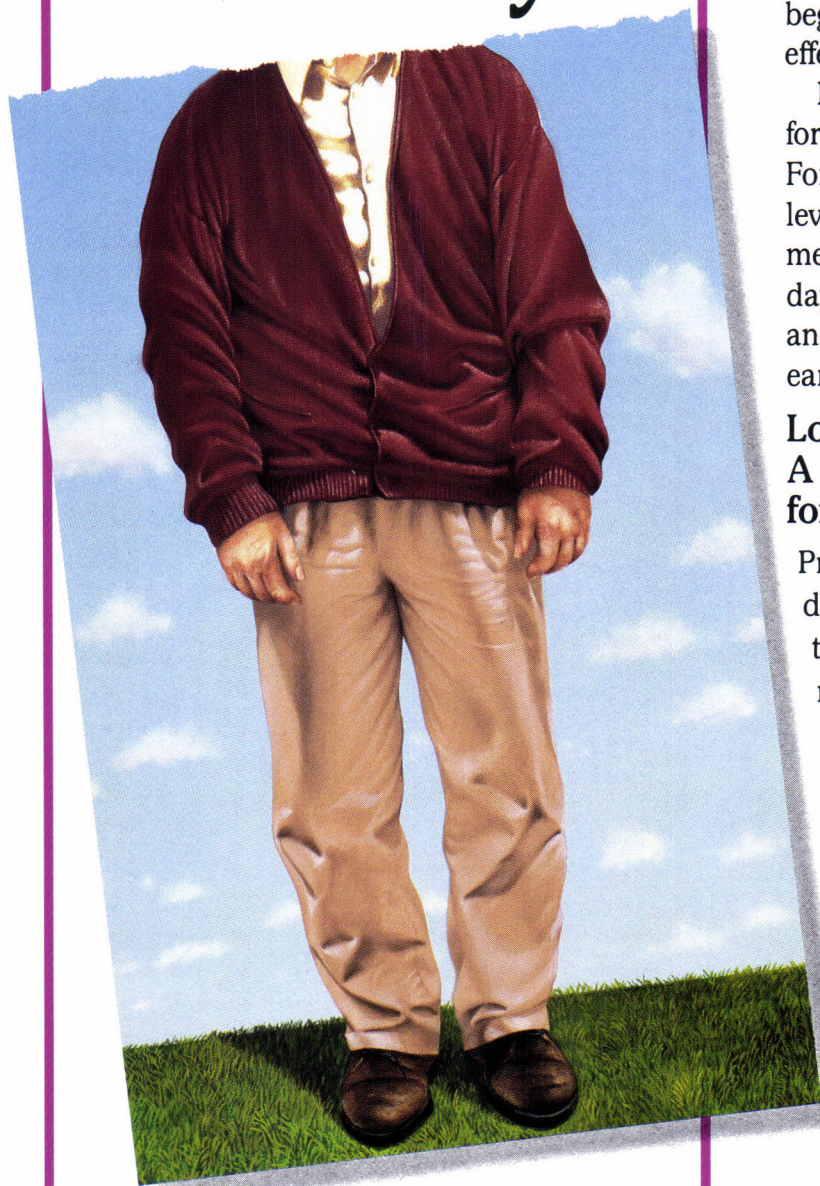
**REFERENCES** 1. Hass WK et al. Ticlopidine Aspirin Stroke Study (TASS). A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989;321:501-507. 2. Ticlopidine Aspirin Stroke Study (TASS). Data on file, Syntex Inc., Vol. 52, Oct 1989. 3. Ticlid product monograph. 4. B'lier J, Love B. Recent therapeutic options for stroke prevention. *Hospital Physician* 1991; Vol. 27,(6)13-24. 5. Canadian American Ticlopidine Study (CATS). Data on file, Syntex Inc., Vol. 70, Oct 1989. 6. Gent M et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *The Lancet* 1989 Jun;1215-20.

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TE-9210  



# Low-dose Prolopa. Benefits for the brain and the body.



The newest therapy recommendations for Parkinson's disease are to begin levodopa therapy at the lowest effective dose.

Not all levodopa combinations are formulated to be used at low doses.\* For example, the manufacturer of 100 levodopa/25 carbidopa (MSD) recommends the equivalent of 3 tablets per day<sup>1</sup> to reduce the incidence of nausea and vomiting so often associated with early levodopa therapy.<sup>1</sup>

## **Low-dose Prolopa (50/12.5). A unique levodopa formulation for few G.I. side effects.**

Prolopa uses a different peripheral decarboxylase inhibitor.<sup>1</sup> It allows you to start therapy with the lowest recommended levodopa dosage and a low incidence of nausea and vomiting.<sup>2</sup>

Consider initiating with Prolopa. For early Parkinson's control with a lower dose.

**P PROLOPA<sup>®</sup>**  
**50/12.5**  
(levodopa 50 mg / benserazide 12.5 mg)

## Levodopa that starts lower.

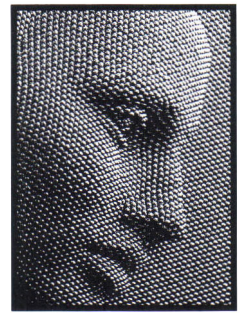
\*Less than 300 mg of levodopa per day

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For brief prescribing information see pages xxvii and xxviii

(xxiii)





# Prescribing Information

## ACTION AND CLINICAL PHARMACOLOGY

SIBELIUM® (flunarizine hydrochloride) prevents the deleterious effects of cellular calcium overload by reducing excessive transmembrane fluxes of calcium. Flunarizine does not interfere with normal cellular calcium homeostasis. Flunarizine also has antihistaminic properties.

The effects of flunarizine in the prophylaxis of migraine are most pronounced with regards to the reduction of the frequency of attacks. The severity of migraine attacks improves to a lesser extent, while little or no effect is seen on the duration of migraine episodes.

The pharmacokinetic parameters of orally administered flunarizine are summarized in Table 1.

Flunarizine is well absorbed; peak plasma levels are attained 2 to 4 hours after oral administration in healthy volunteers. Plasma concentrations increase gradually during chronic administration of 10 mg daily, reaching a steady state level after 5 to 6 weeks of drug administration. Steady state plasma levels remain constant during prolonged treatment although there is substantial interindividual variation; plasma levels range between 39 and 115 ng/mL.

In 50 elderly patients (mean age 61 years), with intermittent claudication, long term (median 6 months) treatment with flunarizine, 10 mg per day, yielded fairly constant steady state plasma levels albeit with considerable interindividual differences. While plasma flunarizine levels were between 50 ng/mL and 100 ng/mL, in 46% of patients, individual values ranged from less than 20 ng/mL to 580 ng/mL. Flunarizine was devoid of cumulative effects as shown by repeated measurements.

As indicated by the large apparent volume of distribution (mean = 43.2 L/kg; range = 26.7 – 79.9 L/kg) seen after the oral administration of 30 mg in healthy volunteers, flunarizine is extensively distributed to tissues. Drug concentrations in tissues, particularly adipose tissue and skeletal muscle, were several times higher than plasma levels.

Flunarizine is 99.1% bound; 90% is bound to plasma proteins and 9% distributed to blood cells, leaving less than 1% present as free drug in the plasma water.

Flunarizine is metabolized principally through N-oxidation and aromatic hydroxylation. During a 48 hour period after a single 30 mg dose, minimal urinary (< 0.2%) and fecal (< 6%) excretion of flunarizine and/or its metabolites was found. This indicates that the drug and its metabolites are excreted very slowly over a prolonged period of time.

Flunarizine has a long elimination half-life of about 19 days.

Table 1: Pharmacokinetic parameters of flunarizine in healthy volunteers

No. of Doses	Dose (mg)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC (ng/mL·h)	t <sub>1/2α</sub> (h)	Cl <sub>p</sub> (mL/min)	t <sub>1/2β</sub> (mean days) [range]
Single Dose Studies	5	30.5	2-4	133 <sup>a</sup>	2.4	443.7	4 [2-8]
	10	81.5		615 <sup>b</sup>	2.8		
	20	117.0	1091 <sup>c</sup>	3.6			
	30	81.6	1169 <sup>d</sup>	5			
Multiple Dose Studies	14	5	2-6	18.1 <sup>b</sup>	301.2	[4-19]	
	14	10		38.8 <sup>b</sup>			
	14	15		68.4 <sup>b</sup>			
	57	10		114.5			1678 <sup>d</sup>

a Area under curve 0 to 8 hours  
b Plasma concentrations at 2 hours  
c Area under curve 0 to 168 hours  
d Area under curve 0 to 24 hours

## INDICATIONS AND CLINICAL USE

SIBELIUM (flunarizine hydrochloride) is indicated in the prophylaxis of classic and common migraine. The safety of flunarizine in long-term use (i.e. for more than 4 months) has not been systematically evaluated in controlled clinical trials. Flunarizine is not indicated in the treatment of acute migraine attacks.

## CONTRAINDICATIONS

SIBELIUM (flunarizine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug. Flunarizine is contraindicated in patients with a history of depression or pre-existing extrapyramidal disorders.

## WARNINGS

Clinical studies indicate that flunarizine treatment, even at recommended doses, can produce motor disturbances in subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease, however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely and monitored at regular intervals so that extrapyramidal symptoms may be detected early, and if necessary, treatment discontinued.

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression, mostly in younger patients.

## PRECAUTIONS

Since sedation and/or drowsiness occur in some patients during treatment with SIBELIUM (flunarizine hydrochloride) (see ADVERSE REACTIONS), patients should be cautioned against activities which require alertness or rapid, precise responses (e.g. operating machinery or a motor vehicle) until the response to the drug has been determined.

## Use in Pregnancy

To date, there are no data to support the use of flunarizine during pregnancy. It should therefore not be administered to pregnant women unless the anticipated benefits outweigh the potential risks.

## Use During Lactation

Studies in lactating dogs have shown that flunarizine is excreted in milk. The concentration of flunarizine in milk is much greater than that in plasma. Breast feeding should therefore be discouraged in women taking flunarizine.

## Use in the Elderly

The efficacy of flunarizine in the prophylaxis of migraine has not been established in elderly subjects.

## Use in Children

The efficacy of flunarizine in the prophylaxis of migraine has not been established in patients younger than 18 years of age.

## Use in Patients with Parkinson's Disease

Flunarizine is contraindicated in patients with pre-existing Parkinson's disease or other extrapyramidal disorders (see CONTRAINDICATIONS). Clinical studies indicate that prolonged flunarizine treatment, even at recommended doses, can produce motor disturbances in elderly subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely so that extrapyramidal symptoms may be detected early and if necessary, treatment discontinued.

## Use in Depressive Patients

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression mostly in younger patients (see CONTRAINDICATIONS).

## Endocrine Effects

Galactorrhea has been reported in a few female patients, some of whom were also on oral contraceptives, within the first two months of flunarizine treatment. Discontinuation of flunarizine therapy resolved the galactorrhea in most cases. Flunarizine therapy caused a mild but significant elevation of serum prolactin levels while GH, LH, FSH and TSH levels did not show significant variation. Two cases of menstrual irregularities have been reported.

## Drug Interactions

Evidence from therapeutic trials in epileptic patients indicates that whereas flunarizine does not affect the kinetics of phenytoin, carbamazepine and valproic acid, it does decrease the plasma levels of mephenytoin. Furthermore, steady state levels of flunarizine are reduced by coadministration of two or more anticonvulsants. This is considered to be a result of enhanced first pass metabolism of flunarizine as a consequence of liver enzyme induction by the anticonvulsant medications.

In other studies, flunarizine was shown not to affect the anticoagulant effect of warfarin sodium or the hypoglycemic effect of glibenclamide and insulin.

## Use in Patients with Impaired Hepatic Function

Flunarizine is metabolised by the liver, therefore care should be exercised when flunarizine is given to patients with compromised liver function.

## ADVERSE REACTIONS

In clinical trials with SIBELIUM (flunarizine hydrochloride) migraine patients, drowsiness (also described as sedation or fatigue) as well as weight gain (and/or increased appetite) occurred fairly frequently, in the order of 20 and 15%, respectively. Of 840 migraine patients, 23 (2.7%) and 9 (1.1%) required withdrawal from flunarizine therapy due to drowsiness and weight gain, respectively.

The most serious side effect encountered in migraineurs during clinical trials was depression. Of 840 migraine patients, 11 (1.3%) were withdrawn due to depression. International post-marketing experience suggests that patients between 20 and 54 years of age with a personal or familial history of depression are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Clinical experience in other indications and epidemiologic surveys suggest that extrapyramidal symptoms may develop during flunarizine therapy. Elderly patients are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Other side effects encountered in clinical trials for migraine prophylaxis included the following:

Gastrointestinal: Heartburn, nausea, emesis, gastralgia;  
Central Nervous System: Insomnia and sleep change, anxiety, dizziness/vertigo;  
Miscellaneous: Dry mouth, asthenia, muscle aches, skin rash

## SYMPTOMS AND TREATMENT OF OVERDOSE

There has been no experience to date with overdosage of SIBELIUM (flunarizine hydrochloride). Based on the pharmacological properties of the drug, sedation and asthenia may be expected to occur. Treatment should consist of induction of emesis or gastric lavage and supportive measures.

## DOSAGE AND ADMINISTRATION

The usual adult dosage of SIBELIUM (flunarizine hydrochloride) 10 mg per day administered in the evening. Patients who experience side effects may be maintained on 5 mg HS.

## Duration of Therapy

Clinical experience indicates that the onset of effect of flunarizine is gradual and maximum benefits may not be seen before the patient has completed several weeks of continuous treatment. Therapy therefore should not be discontinued for lack of response before an adequate time period has elapsed, e.g. 6-8 weeks.

## DOSAGE FORMS

Composition: Each red and grey capsule contains 5 mg flunarizine (as hydrochloride).  
Availability: SIBELIUM flunarizine hydrochloride capsules are available in blister packages of 60 capsules.  
Storage: SIBELIUM capsules 5 mg should be stored at or below 25°C, protected from light and moisture.

Product monograph available on request.

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once-a-day  
**SIBELIUM**  
flunarizine

See pages iv and v



# Epival<sup>®</sup>

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.

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 immediately 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). Hyperglycemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycemia.

**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; peach-coloured tablets of 250 mg; lavender-coloured tablets of 500 mg. Supplied in bottles of 100 tablets.

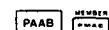
Table of Initial Doses by Weight (based on 15 mg/kg/day)

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



## Brief Prescribing Information

**TEGRETOL®** (carbamazepine tablets)  
TEGRETOL® 200 mg

**TEGRETOL® Chewtabs**  
(carbamazepine chewable tablets)  
TEGRETOL® Chewtabs™ 100 mg  
TEGRETOL® Chewtabs™ 200 mg

**TEGRETOL® CR** (carbamazepine controlled release tablets)  
TEGRETOL® CR 200 mg TEGRETOL® CR 400 mg  
Anticonvulsant for symptomatic relief of trigeminal neuralgia

**ACTION** TEGRETOL (carbamazepine) has anticonvulsant properties which have been found useful in the treatment of psychomotor epilepsy and, as an adjunct in the treatment of partial epilepsies, when administered in conjunction with other anticonvulsant drugs to prevent the possible generalization of the epileptic discharge. A mild psychotropic effect has been observed in some patients, which seems related to the effect of the carbamazepine in psychomotor or temporal lobe epilepsy. Carbamazepine relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours. Like other tricyclic compounds, carbamazepine has a moderate anticholinergic action which is responsible for some of its side effects. A tolerance may develop to the action of carbamazepine after a few months of treatment and should be watched for. Carbamazepine may suppress ventricular automaticity due to its membrane-depressant effect similar to that of quinidine and procainamide, associated with suppression of phase 4 depolarization of the heart muscle fiber. A number of investigators have reported a deterioration of EEG abnormalities with regard to focal alterations and a higher incidence of records with nil  $\beta$  activity, during carbamazepine-combined treatment. The absorption of carbamazepine in man is relatively slow. When taken in a single oral dose, TEGRETOL (carbamazepine tablets) and TEGRETOL CHEWTABS (carbamazepine chewable tablets) yield peak plasma concentrations of unchanged carbamazepine within 4-24 hours. With respect to the quantity of carbamazepine absorbed, there is no clinically relevant difference between the various dosage forms. When TEGRETOL CR (carbamazepine controlled release tablets) are administered repeatedly, they yield a lower average maximal concentration of carbamazepine in the plasma, without a reduction in the average minimal concentration. This tends to result in a lower incidence of intermittent concentration-dependent adverse drug reactions. It also ensures that the plasma concentrations remain largely stable throughout the day, thereby making it possible to manage with a twice-daily dosage. Carbamazepine becomes bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in the saliva reflects the non-protein-bound portion present in the serum (20-30%). The elimination half-life of unchanged carbamazepine in the plasma averages approximately 36 hours following a single oral dose, whereas after repeated administration, which leads to autoinduction of hepatic enzymes, it averages only 16-24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing anti-epileptic agents, half-life values average 9-10 hours have been found. Only 2-3% of the dose, whether given singly or repeatedly, is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active 10,11-epoxide. In man, the main urinary metabolite of carbamazepine is the transdiol derivative originating from the 10,11-epoxide; a small portion of the epoxide is converted into 9-hydroxymethyl-10-carbamoyl-acridan. Other important biotransformation products are various monohydroxylated compounds, as well as the N-glucuronide of carbamazepine. The therapeutic range for the steady-state plasma concentration of carbamazepine generally lies between 4-10  $\mu$ g/ml.

**INDICATIONS AND CLINICAL USE** **A. Trigeminal Neuralgia:** TEGRETOL (carbamazepine) is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, TEGRETOL has relieved glossopharyngeal neuralgia. For patients who fail to respond to TEGRETOL, or who are sensitive to the drug, recourse to other accepted measures must be considered. Carbamazepine is not a simple analgesic and should not be used to relieve trivial facial pains or headaches. **B. TEGRETOL has been found useful in:** 1. the management of psychomotor (temporal lobe) epilepsy and, 2. as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication. 3. as an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs. Carbamazepine is not effective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge. Moreover, exacerbation of seizures may occasionally occur in patients with atypical absences.

**CONTRAINDICATIONS** TEGRETOL (carbamazepine) should not be administered to patients with a history of hepatic disease, acute intermittent porphyria, or serious blood disorder. TEGRETOL should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer TEGRETOL to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of TEGRETOL should be low initially, and increased very gradually. TEGRETOL should not be administered to patients presenting atrioventricular heart block. (See Sections on ACTION and PRECAUTIONS). TEGRETOL should not be administered to patients with known hypersensitivity to carbamazepine or to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites, because of the similarity in chemical structure.

**WARNINGS** Although reported infrequently, serious adverse effects have been observed during the use of TEGRETOL (carbamazepine). Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis have also been reported. If it, therefore, important that TEGRETOL should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia. TEGRETOL should be discontinued if any evidence of significant bone marrow depression appears. (See "Precautions"). Should signs and symptoms suggest a severe skin reaction such as Steven-Johnson syndrome or lyell syndrome, TEGRETOL should be withdrawn at once. Long-term toxicity studies in rats indicated a potential carcinogenic risk. Therefore the possible risk of the drug must be weighed against the potential benefits before prescribing

TEGRETOL to individual patients. **Pregnancy and nursing:** Women with epilepsy who are, or intend to become pregnant, should be treated with special care. In women of childbearing potential, TEGRETOL (carbamazepine) should, whenever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with more than one anti-epileptic drug (e.g. valproic acid plus carbamazepine plus phenobarbitone and/or phenytoin) is greater than in those of women receiving a single anti-epileptic. Minimum effective doses should be given and the plasma levels monitored. If pregnancy occurs in a woman receiving TEGRETOL, or if the problem of initiating TEGRETOL arises during pregnancy, the drug's potential benefits must be weighed against its hazards, particularly during the first 3 months of pregnancy. TEGRETOL should not be discontinued or withheld from patients if required to prevent major seizures because of the risks posed, to both mother and fetus, by status epilepticus with attendant hypoxia. The possibility that carbamazepine, like all major anti-epileptic drugs, increases the risk of malformations has been reported. There are rare reports on developmental disorders and malformations, including spina bifida, in association with carbamazepine. Conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. Folic acid deficiency is known to occur in pregnancy. Anti-epileptic drugs have been reported to aggravate folic acid deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy. To prevent neonatal bleeding disorders, Vitamin K<sub>1</sub> administration to the mother during the last weeks of pregnancy, as well as to the newborn, has been recommended. Carbamazepine passes into breast milk in concentrations of about 25-60% of the plasma level. No reports are available on the long-term effect of breast feeding. The benefits of breast feeding should be weighed against the possible risks to the infant. Should the mother taking carbamazepine nurse her infant, the infant must be observed for possible adverse reactions, e.g. somnolence. A severe hypersensitivity skin reaction in a breast-fed baby has been reported. It should be noted that the reliability of oral contraceptives may be adversely affected by carbamazepine (see Precautions, Drug Interactions).

**PRECAUTIONS (Clinical Monitoring of Adverse Reactions:** TEGRETOL (carbamazepine) should be prescribed only after a critical risk-benefit appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematological reactions to other drugs, or interrupted courses of therapy with TEGRETOL. Careful clinical and laboratory supervision should be maintained throughout treatment. Should any signs or symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, TEGRETOL should be immediately discontinued until the case is carefully reassessed. (a) **Bone marrow function:** Complete blood counts, including platelets and possibly reticulocytes and serum iron, should be carried out before treatment is instituted. Suggested guidelines for monitoring are weekly for the first month, then monthly for the next five months, thereafter 2-4 times a year. If definitely low or decreased white blood cell or platelet counts are observed during treatment, the patient and the complete blood count should be monitored closely. Non-progressive fluctuating asymptomatic leucopenia, which is encountered, does not generally call for the withdrawal of TEGRETOL. However, treatment with TEGRETOL should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g. fever or sore throat, as this could indicate the onset of significant bone marrow depression. Because the onset of potentially serious blood dyscrasias may be rapid, patients should be made aware of early toxic signs and symptoms of a potential hematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage appear, the patient should be advised to consult his/her physician immediately. (b) **Hepatic function:** Baseline and periodic evaluations of hepatic function must be performed, particularly in elderly patients and patients with a history of liver disease. TEGRETOL should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease. (c) **Kidney function:** Pretreatment and periodic complete urinalysis and BUN determinations should be performed. (d) **Ophthalmic examinations:** Carbamazepine has been associated with pathological eye changes. Periodic eye examinations, including slit-lamp funduscopy and tonometry are recommended. (e) **Plasma levels:** Although correlations between dosage and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity, especially where more than one drug is being used (see "Interactions"). **Increased seizure frequency:** TEGRETOL should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since its use has been associated with increased frequency of generalized convulsions. In case of exacerbation of seizures, TEGRETOL should be discontinued. **Dermatologic:** Mild skin reactions, e.g. isolated macular or maculopapular exanthema, usually disappear within a few days or weeks, either during continued course of treatment or following a decrease in dosage. However, the patient should be kept under close surveillance because of the rare possibility of Steven-Johnson syndrome or Lyell's syndrome occurring (see WARNINGS). **Urinary Retention and Increased Intraocular Pressure:** Because of its anticholinergic action, carbamazepine should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug. **Occurrence of Behavioural Disorders:** Because it is closely related to the other tricyclic drugs, there is some possibility that carbamazepine might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in alcoholics. **Use in Patients with Cardiovascular Disorders:** TEGRETOL should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, an ECG should be performed before administering TEGRETOL, in order to exclude patients with atrioventricular block. **Driving and Operating Hazardous Machinery:** Because dizziness and drowsiness are possible side effects of TEGRETOL, patients should be warned about the possible hazards of operating machinery or driving automobiles. **Drug Interactions:** Induction of hepatic enzymes in response to carbamazepine may have the effect of diminishing or abolishing the activity of certain drugs that are also metabolized in the liver. The dosage of the following drugs may have to be adjusted when administered with TEGRETOL: clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids (e.g. prednisolone, dexamethasone), cyclosporin, digoxin, doxycycline, flodipine, haloperidol, thioridazine, imipramine, methadone, oral contraceptives, theophylline, and oral anticoagulants (warfarin, phenprocoumon, dicumarol). Phenytoin plasma levels have been reported both to be raised and lowered by carbamazepine, and mephenytoin plasma levels have been reported in rare

instances to increase. The following drugs have been shown to raise plasma carbamazepine levels: erythromycin, troleandomycin, possibly josamycin, isoniazid, verapamil, diltiazem, propoxyphene, vloxazine, fluoxetine, cimetidine, acetazolamide, danazol, and possibly desipramine. Nicotinamide raises carbamazepine plasma levels in children, but only at high dosage in adults. Since an increase in carbamazepine plasma levels may result in unwanted effects (e.g. dizziness, drowsiness, ataxia, diplopia and nystagmus), the dosage of TEGRETOL should be adjusted accordingly and the blood levels monitored. The plasma levels of carbamazepine may be reduced by phenobarbitone, phenytoin, primidone, progabide, or theophylline, and possibly by clonazepam. On the other hand, valproic acid, valpromide, and primidone have been reported to raise plasma levels of the pharmacologically active metabolite, carbamazepine-10,11 epoxide. The dose of TEGRETOL may consequently have to be adjusted. Combined use of TEGRETOL with lithium, metoclopramide, or haloperidol, may increase the risk of neurotoxic side effects (even in the presence of "therapeutic plasma levels"). Concomitant use of TEGRETOL and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. TEGRETOL, like other anticonvulsants, may adversely affect the reliability of oral contraceptives; breakthrough bleeding may occur. Patients should accordingly be advised to use some alternative, non-hormonal method of contraception. Concomitant medication with TEGRETOL and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia. Carbamazepine may antagonize the effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage may need to be raised and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected. Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and its active 10,11-epoxide; carbamazepine plasma levels should be monitored. Carbamazepine, like other psycho-active drugs, may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol consumption during treatment. TEGRETOL should not be administered in conjunction with a MAO inhibitor. (See CONTRAINDICATIONS).

**ADVERSE REACTIONS** The reactions which have been most frequently reported with TEGRETOL (carbamazepine) are CNS (e.g. drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions. These reactions usually occur only during the initial phase of therapy, if the initial dose is too high, or when treating elderly patients. They have rarely necessitated discontinuing TEGRETOL therapy, and can be minimized by initiating treatment at a low dosage. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and possibly lower the daily dose and/or divide it into 3-4 fractional doses. The more serious adverse reactions observed are the hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy. If treatment with TEGRETOL has to be withdrawn abruptly, the change-over to another anti-epileptic drug should be effected under cover of diazepam. The following adverse reactions have been reported: **Hematologic:** Occasional or frequent - leucopenia; occasional - eosinophilia, thrombocytopenia; rare - leucocytosis, lymphadenopathy; isolated cases - agranulocytosis, aplastic anemia, pure red cell aplasia, macrocytic anemia, acute intermittent porphyria, reticulocytosis, folic acid deficiency, thrombocytopenic purpura, and possibly hemolytic anemia. In a few instances, deaths have occurred. **Hepatic:** frequent - elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant; occasional - elevated alkaline phosphatase; rarely - transaminases; rare - jaundice, hepatitis of cholestatic, parenchymal, hepatocellular, or mixed type; isolated cases - granulomatous hepatitis. **Dermatologic:** occasional to frequent - skin sensitivity reactions and rashes, erythematous rashes, urticaria; rare - exfoliative dermatitis and erythroderma, Steven-Johnson syndrome, systemic lupus erythematosus-like syndrome; isolated cases - toxic epidermal necrolysis (Lyell's syndrome), photosensitivity, erythema multiforme and nodosum, skin pigmentation changes, pruritus, purpura, acne, diaphoresis, alopecia and neurodermatitis. **Neurologic:** frequent - vertigo, somnolence, ataxia and fatigue. Occasionally - an increase in motor seizures (see INDICATIONS), headache, diplopia, nystagmus, accommodation disorders (e.g. blurred vision); rare - abnormal involuntary disorders (e.g. tremor, asterixis, orofacial dyskinesia, choreoathetosis disorders, dystonia, tics); isolated cases - oculomotor disturbances, speech disorders (e.g. dysarthria or slurred speech), peripheral neuritis, paraesthesiae. There have been some reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of TEGRETOL could be established. **Cardiovascular:** Disturbances of cardiac conduction, bradycardia, arrhythmias. Stokes-Adams in patients with AV-block, congestive heart failure, hypertension or hypotension, aggravation of coronary artery disease, thrombophlebitis, thromboembolism. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds. **Psychiatric:** Isolated cases - hallucinations (visual or acoustic), depression, sometimes with talkativeness, agitation, loss of appetite, restlessness, aggressive behaviour, confusion, activation of psychosis. **Genitourinary:** Isolated cases - interstitial nephritis and renal failure, as well as signs of renal dysfunction (e.g. albuminuria, glycosuria, hematuria, oliguria sometimes associated with elevated blood pressure, and elevated BUN/azotemia), urinary frequency, urinary retention, and renal failure. Isolated reports - sexual disturbances/impotence. **Gastrointestinal:** Occasional or frequent - nausea, vomiting. Occasional: dryness of the mouth and throat; rare - diarrhoea or constipation; isolated cases - abdominal pain, glossitis, stomatitis, anorexia. **Sense organs:** Isolated cases - lens opacities, conjunctivitis, retinal changes, tinnitus, hyperacusis, and taste disturbances. **Endocrine system and metabolism:** Occasionally edema, fluid retention, weight increase, hyponatremia and reduced plasma osmolality due to antidiuretic hormone (ADH)-like effect occurs, leading in isolated cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities. Isolated cases of gynaecomastia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine i.e. FT<sub>4</sub>, T<sub>4</sub>, T<sub>3</sub>, and increased TSH, usually without clinical manifestations), disturbances of bone metabolism (decrease in plasma calcium and 25-OH-calciferol), leading in isolated cases to osteomalacia, as well as reports of elevated levels of cholesterol, including HDL cholesterol and triglycerides. **Musculoskeletal system:** Isolated cases - arthralgia, muscle pain or cramp. **Respiratory:** Isolated cases - pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia. **Hypersensitivity reactions:** A rare delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests; occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium). Isolated cases: aseptic meningitis; with myoclonus and eosinophilia; anaphylactic reaction. Treatment should be discontinued should such hypersensitivity reactions occur.



**SYMPTOMS AND TREATMENT OF OVERDOSAGE** Lowest known lethal dose: estimated 3.2g (24 year old woman). Highest known doses survived: 80g (34 year old man); 34g (13 year old girl); 1.4g (23 month old girl). **Symptoms of Overdosage:** The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, and respiratory systems. Central nervous system: CNS depression, disorientation, tremor, restlessness, somnolence, agitation, hallucination, coma, blurred vision, nystagmus, mydriasis, slurred speech, dysarthria, ataxia, dyskinesia, abnormal reflexes (slowed/hyperactive), convulsions, psychomotor disturbances, myoclonus, opisthotonia, hyperthermia/hypothermia, flushed skin/cyanosis, EEG changes. Respiratory system: respiratory depression, pulmonary edema. Cardiovascular system: tachycardia, hypotension/hypertension, conduction disturbance with widening of QRS complex, syncope in association with cardiac arrest. Gastrointestinal system: nausea, vomiting, delayed gastric emptying, reduced bowel motility. Renal function: urinary retention, oliguria or anuria; fluid retention, and water intoxication. Laboratory findings: hyponatremia, hypokalemia, leukocytosis, reduced white cell count, metabolic acidosis, hyperglycemia, glycosuria, acetonuria, increased muscle creatinine phosphokinase. **Treatment of Overdosage:** There is no known specific antidote to TEGRETOL (carbamazepine). Evacuate the stomach, with an emetic or by gastric lavage, then administer activated charcoal. Vital signs should be watched and symptomatic treatment should be administered as required. Hyperirritability or convulsions may be controlled by the administration of parenteral diazepam or barbiturates but they may induce respiratory depression, particularly in children. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression. When barbiturates are employed, it is advisable to have equipment available for artificial ventilation and resuscitation. Barbiturates should not be used if drugs that inhibit monoamine oxidase have been taken by the patient, either in overdosage or in recent therapy (within two weeks). Hyponatremia should be treated by restricting fluids and a slow and careful NaCl 0.9% infusion i.v. These measures may be useful in preventing brain damage. Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids. For hypotension unresponsive to measures taken to increase plasma volume, dopamine or dobutamine i.v. may be administered. It is recommended that the electrocardiogram be monitored, particularly in children, to detect any cardiac arrhythmias or conduction defects. Charcoal hemoperfusion has been recommended. Forced diuresis, hemodialysis, and peritoneal dialysis have been reported to be ineffective. Relapse and aggravation of the symptomatology on the 2nd or 3rd day after overdosage, due to delayed absorption, should be anticipated.

**DOSAGE AND ADMINISTRATION Use in Epilepsy (See INDICATIONS):** A low initial daily dosage of TEGRETOL (carbamazepine) with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient. TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals whenever possible. The controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid during or after a meal. These controlled release tablets should be prescribed as a twice-daily dosage. If necessary, three divided doses may be prescribed. **Adults and Children Over 12 Years of Age:** Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, in divided doses, until the best response is obtained. The usual optimal dosage is 800 to 1200 mg daily. In rare instances some adult patients have received 1600 mg. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached. **Children 6-12 Years of Age:** Initially, 100 mg in divided doses on the first day. Increase gradually by adding 100 mg per day until the best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached. **Use in Trigeminal Neuralgia:** The initial daily dosage should be small: 200 mg taken in 2 doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg/day until relief of pain is obtained. This is usually achieved at dosage between 200 and 800 mg daily, but occasionally up to 1200 mg/day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimal effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of TEGRETOL at intervals of not more than 3 months, depending upon the individual clinical course. Prophylactic use of the drug in trigeminal neuralgia is not recommended.

**AVAILABILITY TEGRETOL Tablets 200 mg:** Each white, round, flat, bevelled-edge, double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Available in bottles of 100 and 500 tablets. **TEGRETOL Chew-tabs 100 mg:** Pale pink, round, flat, bevelled-edge tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each chewable tablet contains 100 mg carbamazepine. Available in bottles of 100 Chew-tabs. **TEGRETOL Chew-tabs 200 mg:** Pale pink, oval, biconvex tablets with distinct red spots. GEIGY engraved on one side and PU engraved on the other. Fully bisected between the P and U. Each chewable tablet contains 200 mg carbamazepine. Available in bottles of 100 Chew-tabs. **TEGRETOL CR 200 mg:** Beige-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and HC/HC on the other. Fully bisected on both sides. Each controlled release tablet contains 200 mg carbamazepine. Available in bottles of 100 tablets. **TEGRETOL CR 400 mg:** Brownish-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully bisected on both sides. Each controlled release tablet contains 400 mg carbamazepine. Available in bottles of 100 tablets. Protect from heat and humidity. TEGRETOL is available to patients only by prescription. Product Monograph available upon request.

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**Geigy**

Mississauga, Ontario L5N 2W5 September, 1991



**PROLOPA® 50/12.5**  
levodopa 50 mg benserazide 12.5 mg

**Rx Summary**  
**Antiparkinsonian Agent**  
**Indications**

Treatment of Parkinson's syndrome when not drug induced.

**Contraindications**

Known hypersensitivity to levodopa or benserazide; in patients in whom sympathomimetic agents are contraindicated; concomitantly with, or within 2 weeks of, MAOI administration; uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; narrow-angle glaucoma.

**Warnings**

Discontinue levodopa at least 12 hours before initiating "Prolopa". See Dosage section for substitution recommendations.

Not indicated in intention tremor, Huntington's chorea or drug-induced Parkinsonism.

Increase dosage gradually to avoid CNS side effects (involuntary movements). Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Caution in patients with history of psychotic disorders or receiving psychotherapeutic agents.

In patients with atrial, nodal or ventricular arrhythmias or history of myocardial infarction initiate treatment cautiously in hospital. Caution in patients with history of melanoma or suspicious undiagnosed skin lesions. Safety in patients under 18 years has not been established. In women who are or may become pregnant, weigh benefits against possible hazards to mother and fetus. Not recommended for nursing mothers.

**Precautions**

Monitor cardiovascular, hepatic, hematopoietic and renal function during extended therapy. Caution in patients with history of convulsive disorders. Upper gastrointestinal hemorrhage possible in patients with a history of peptic ulcer.

Normal activity should be resumed gradually to avoid risk of injury.

Monitor intraocular pressure in patients with chronic wide-angle glaucoma. Pupillary dilation and activation of Horner's syndrome have been reported rarely. Exercise caution and monitor blood pressure in patients on anti-hypertensive medication. "Prolopa" can be discontinued 12 hours prior to anesthesia. Observe patients on concomitant psychoactive drugs for unusual reactions.

**Adverse Reactions**

Most common are abnormal involuntary movements, usually dose dependent, which necessitate dosage reduction. Other serious reactions are periodic oscillations in performance (end of dose akinesia, on-off phenomena and akinesia paradoxa) after prolonged therapy, psychiatric disturbances (including paranoia, psychosis, depression, dementia, increased libido, euphoria, sedation and stimulation), and cardiovascular effects (including arrhythmias, orthostatic hypotension, hypertension, ECG changes and angina pectoris).

Neurologic, intellectual, gastrointestinal, dermatologic, hematologic, musculoskeletal, respiratory, genitourinary and ophthalmologic reactions have also been reported. Consult Product Monograph for complete list.

**Dosage**

**Individualize therapy and titrate in small steps to maximize benefit without dyskinesias. Do not exceed the recommended dosage range.**

Initially, one capsule "Prolopa" 100-25 once or twice daily, increased carefully by one capsule every third or fourth day (slower in post-encephalitic Parkinsonism) until optimum therapeutic effect obtained without dyskinesias. At upper limits of dosage, increment slowly at 2-4 week intervals. Administer with food.

**Optimal dosage is usually 4-8 "Prolopa" 100-25 capsules daily, in 4-6 divided doses.**

"Prolopa" 200-50 capsules are intended for maintenance therapy once optimal dosage has been determined using "Prolopa" 100-25 capsules. No patient should receive more than 1000-1200 mg levodopa daily during the first year of treatment. "Prolopa" 50-12.5 capsules should be used when frequent dosing is required to minimize adverse effects.

For patients previously treated with levodopa, allow at least 12 hours to elapse and initiate "Prolopa" at 15% of previous levodopa dosage. During maintenance, reduce dosage slowly, if possible, to a maximum of 600 mg levodopa daily.

**Supply**

"Prolopa" 50-12.5 capsules containing 50 mg levodopa and 12.5 mg benserazide. Contains mannitol.

"Prolopa" 100-25 capsules containing 100 mg levodopa and 25 mg benserazide.

"Prolopa" 200-50 capsules containing 200 mg levodopa and 50 mg benserazide.

Bottles of 100.

Product Monograph available on request.

**References**

1. Da Prada, M. (1984). Peripheral decarboxylase inhibition: a biochemical comparison between benserazide and carbidopa. *Parkinson's Disease: Actual Problems and Management*. Basie Symposium, Editores Roche, pp25-38.

2. Adapted from Rinne, U.K. et al: Levodopa with benserazide or carbidopa in Parkinson Disease. *Neurology* Dec. 1979; 29(12): 1584-1589.



Hoffmann-La Roche Limited  
Etobicoke, Ontario M9C 5J4



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**ELDEPRYL®**  
selegiline hydrochloride



**Rx Summary**  
**Antiparkinson Agent**

**Indications and clinical use**

As adjunctive therapy with levodopa in the management of Parkinson's disease. Eldepryl is not indicated as first line treatment of Parkinson patients but may be of value as add-on therapy.

**Contraindications**

In patients with known hypersensitivity to Eldepryl. Eldepryl should not be used in patients with active peptic ulcer, extrapyramidal disorders such as excessive tremor or tardive dyskinesia, or patients with severe psychosis or profound dementia. Eldepryl should not be used with meprobamate (Demerol and other trade names). This contraindication is often extended to other opioids.

**Warnings (Selective vs non-selective inhibition of MAO-B)**

Eldepryl should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. It is prudent, in general, to avoid the concomitant use of Eldepryl and fluoxetine (Prozac).

**Warnings to patients**

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of Eldepryl therapy. The patients should be advised not to exceed the daily dose of 10 mg. The risk of using higher doses of Eldepryl should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided.

**Precautions**

Some patients given Eldepryl may experience an exacerbation of levodopa-associated side effects, presumably due to the increased amounts of dopamine reacting with supersensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa by 10-30%.

**Laboratory Tests**

No specific laboratory tests are essential for the management of patients on Eldepryl. Transient or continuing abnormalities with tendency for elevated values in liver function tests have been described in long term therapy. Although serious hepatic toxicity has not been observed, caution is recommended in patients with a history of hepatic dysfunction. Periodic routine evaluation of all patients is however appropriate.

**Drug Interactions**

Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of Eldepryl and other drugs have been reported.

**Use during Pregnancy**

The use of Eldepryl during pregnancy has not been established. Therefore, Eldepryl should be given to a pregnant woman only if the potential benefits outweigh the potential risks.

**Adverse reactions**

THE SIDE EFFECTS OF ELDEPRYL ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. ELDEPRYL MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA, THEREFORE ADJUSTMENT OF THE DOSAGE OF LEVODOPA MAY BE REQUIRED.

ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS / CONFUSION, PARTICULARLY VISUAL HALLUCINATIONS.

Other reactions include nausea, dizziness, faintness, abdominal pain, dry mouth, vivid dreams, dyskinesias and headache.

**Dosage**

The recommended dosage of Eldepryl is 10 mg per day administered orally in divided doses of 5 mg at breakfast and 5 mg at lunch. Doses higher than 10 mg, per day should not be used. There is not evidence that additional benefit will be obtained from the administration of higher doses. When Eldepryl adjunctive therapy is added to the existing levodopa therapeutic regime, a reduction, usually of 10 to 30 % in the dose of levodopa (in some instances a reduction in the dose of Eldepryl to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects.

**Supplied**

Eldepryl 5mg tablets, available in bottles of 60 tablets.

**References**

1. Elizan TS, Moros DA, Yahr MD: Early Combination of Selegiline and Low-Dose Levodopa as Initial Symptomatic Therapy in Parkinson's Disease. *Arch Neurol*, Vol 48, 31-34, January 1991. 2. Yahr MD, Elizan TS, Moros D: Selegiline in the treatment of Parkinson's disease - long term experience. *New Strategies in the Treatment of Parkinson's Disease*. *Acta Neurol Scand*, 126:157-161, 1989. 3. Svartens B, Dupont E, Mikkelsen B, Mogensen P, Rasmussen C, Boesen F, Heinonen E: Selegiline and levodopa in early or moderately advanced Parkinson's disease: a double-blind controlled short and long term study. *New Strategies in the Treatment of Parkinson's Disease*. *Acta Neurol Scand*, 126:147-152, 1989. 4. Heinonen EH, Rinne UK: Selegiline in the treatment of Parkinson's disease. *New Strategies in the Treatment of Parkinson's Disease*. *Acta Neurol Scand*, 1989:126, 103-111. 5. Yahr MD in Lees, A: *Deprenyl in Parkinson's Disease: Guidelines for Clinicians*. *North American Round Table Series*, No. 1, 1-26, 1988. 6. Tetrud JW, Langston JW: Does selegiline (deprenyl) slow the progression of Parkinson's disease? Selegiline therapy in early Parkinson's disease. *Joy* 1990; 13:18. 7. Birkmayer W, Knoll J, Riederer P, Youdim MBH: Deprenyl Leads to Prolongation of L-Dopa Efficacy in Parkinson's Disease. *Mod Probl Pharmacopsych*, Vol 19, 170-176, 1983. 8. Myllylu VV, Santanen KA, Vuorinen J, Heinonen EH: Selegiline (deprenyl) as primary treatment in Parkinson's disease. Selegiline therapy in early Parkinson's disease. *Joy* 1990, 19:24. 9. Marsden CD: Parkinson's disease. *Review Article*. *Lancet* 335 (8695): 948-952, April 1990.

Product Monograph available upon request.



PURDUE FREDERICK INC.  
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**ACTIONS** Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivative with D<sub>2</sub> type dopamine receptor agonist activity, and has also D<sub>1</sub> 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 Turkali, 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, paresthesia, 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 overdose 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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Department of Clinical Neurological Sciences  
University Hospital  
P.O. Box 5339  
London, Ontario N6A 5A5 Canada

## NEUROPATHOLOGIST POSITION

### Sunnybrook Health Science Centre University of Toronto

Candidates with diagnostic, teaching and research experience in neuropathology are invited for the position in the Department of Pathology as of September, 1992. Sunnybrook HSC is a teaching hospital with major programs in Oncology, Trauma, and Aging with ample research opportunity in dementia.

In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents.

For further information contact:

Dr. Shao-nan Huang, Head  
Department of Pathology  
Sunnybrook Health Science Centre  
2075 Bayview Avenue  
North York, Ontario  
M4N 3M5



## SCOTT & WHITE

The Division of Neurological Surgery of Scott & White Clinic and Texas A&M University College of Medicine is seeking a Neurosurgeon to fill a clinical/faculty position as Director of the Division of Neurological Surgery.

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For more information, please call **Barry Harper** at 1-800-725-3627 or send curriculum vitae to:

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2401 South 31st Street  
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## NEUROSURGERY LIONS GATE HOSPITAL North Vancouver, British Columbia

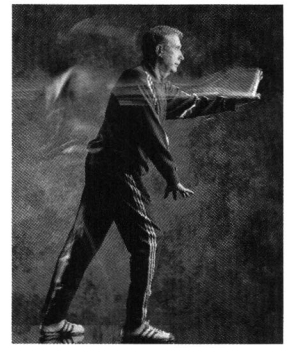
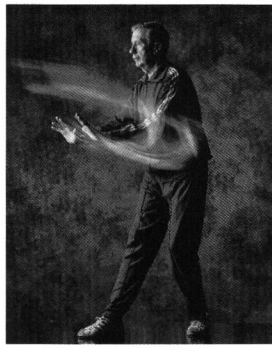
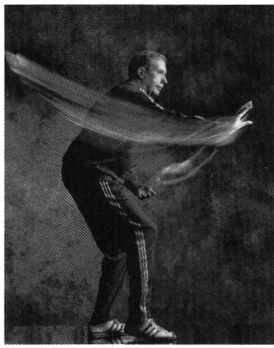
The Division of Neurosurgery of Lions Gate Hospital is seeking a neurosurgeon to fill a vacancy occurring in its three-man neurosurgery team in the summer of 1992.

The 401 acute care bed hospital is located on the north shore of Burrard Inlet in the Greater Vancouver area and provides neurosurgical service for North Vancouver, West Vancouver and Burnaby as well as province wide referrals. The population of North and West Vancouver is 150,000. These are family oriented communities with numerous opportunities for year round recreational activities.

For more information, please call Dr. Stewart Madill at (604) 984-5782 or send curriculum vitae to:

N. Stewart Madill, M.D.  
Vice President, Medical/Diagnostic Services  
Lions Gate Hospital  
231 East 15th Street  
North Vancouver, B.C.  
V7L 2L7





# PR CONTROLLED-RELEASE Sinemet® CR BRINGING BACK CONTROL

(levodopa and carbidopa)

## Controlled Release Tablets Antiparkinson Agent

**Clinical Pharmacology:** SINEMET® CR (levodopa and carbidopa), a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor, is available in a polymer-based controlled-release tablet formulation. SINEMET® CR can be useful in reducing "off" time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had predictable peak dose dyskinesias and unpredictable motor fluctuations.

The symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. While the administration of dopamine is ineffective in the treatment of Parkinson's disease because it does not cross the blood-brain barrier, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier and is converted to dopamine in the basal ganglia. This is thought to be the mechanism whereby levodopa relieves the symptoms of Parkinson's disease.

Levodopa is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Carbidopa, a decarboxylase inhibitor, does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. Combined therapy with levodopa and carbidopa reduces the amount of levodopa required for optimum therapeutic benefit by about 75-80%, permits an earlier response to therapy, and also reduces the incidence of nausea, vomiting and cardiac arrhythmias. Combined therapy, however, does not decrease adverse reactions due to central effects of levodopa.

Following years of treatment with preparations containing levodopa, an increasing number of parkinsonian patients develop fluctuations in motor performance and dyskinesias. The advanced form of motor fluctuations ("on-off" phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

In clinical trials, patients with motor fluctuations experienced reduced "off" time with SINEMET® CR when compared with SINEMET® CR. Global ratings of improvement and activities of daily living in the "on" and "off" states, as assessed by both patient and physician, were slightly better in some patients during therapy with SINEMET® CR than with SINEMET® CR. In patients without motor fluctuations, SINEMET® CR provided therapeutic benefit similar to SINEMET® CR but with less frequent dosing.

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

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

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

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

SINEMET® CR should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hema-

tologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

observed carefully for loss of therapeutic response.

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

*Other drugs:* Although specific interaction studies were not performed with other concomitant drugs, in clinical trials of SINEMET® CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, thiazides, digoxin, H<sub>2</sub> antagonists, salicylates and other nonsteroidal anti-inflammatory drugs. SINEMET® CR was also used with other antiparkinson agents (see DOSAGE AND ADMINISTRATION).

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

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

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

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

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

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

*Nervous System:* Alaxia, numbness, increased hand tremor, muscle

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twitching, blepharospasm, trismus, activation of latent Horner's syndrome.  
**Psychiatric:** Sleepiness, euphoria, paranoid ideation and psychotic episodes, and dementia.

**Cardiovascular:** Arrhythmias, non-specific ECG changes, flushing, phlebitis.  
**Gastrointestinal:** Bitter taste, sialorrhea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

**Integumentary:** Increased sweating, dark sweat, rash, hair loss.

**Genitourinary:** Urinary frequency, retention, incontinence, hematuria, dark urine, nocturia and priapism.

**Special Senses:** Diplopia, dilated pupils, oculogyric crises.

**Miscellaneous:** Weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, hypertension, neuroleptic malignant syndrome, malignant melanoma (see CONTRAINDICATIONS), leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

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

**Laboratory Tests:** Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, and blood urea nitrogen.

Abnormalities in various laboratory tests have occurred with SINEMET® CR and may also occur with SINEMET® CR.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glycosuria.

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

SINEMET® CR may be administered as whole or as half tablets. To maintain the controlled release properties of the product, tablets should not be chewed or crushed.

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

**Initial Dosage and Titration for Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations:** Dosage with SINEMET® CR should be substituted at an amount that eventually provides approximately

10 to 30 percent more levodopa per day. The interval between doses should be prolonged by 30 to 50 percent. Initially, patients should receive SINEMET® CR at a dosage that provides the same amount of levodopa, but with a longer dosing interval. Depending on clinical response, the dosage may be increased.

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

*Guideline for Initial Conversion from SINEMET® to SINEMET® CR*

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

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

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

**Patients Without Prior Levodopa Therapy:** Experience with SINEMET® CR is limited in the *de novo* parkinsonian patients. The initial recommended dose in patients with mild to moderate disease is 1 tablet of SINEMET® CR two times daily.

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

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

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

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

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

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

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

**References:** 1. LeWitt, P.A. et al.: Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): Clinical and pharmacokinetic studies, *Neurology*, 1989, Vol. 39, No. 11, Suppl. 2: 45-53. 2. Data on file; Merck Frosst Canada Inc., SINEMET® CR, Scientific information, 1988. 3. Data on file; Merck Frosst Canada Inc., SINEMET® CR, Physicians Circular, 1990.

**Product Monograph Available on Request**

(352-a.5.91)

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See pages viii and ix



P A A B

# CIBA—GEIGY

## Award for Excellence in Neurological Science

CIBA—GEIGY is offering an Award for Excellence for the best article published in the Journal within the period of one year.

A cash prize of \$2500 will be announced at the annual meeting of the Canadian Congress of Neurological Sciences in June. Articles published in Volume 18 will be adjudicated by the editorial board for the 1991 award.

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**Frisium<sup>®</sup> 10 mg**  
(clobazam)  
**TO ACHIEVE SEIZURE CONTROL**

**Frisium (clobazam) Tablets, 10 mg**  
**THERAPEUTIC CLASSIFICATION** Anticonvulsant for adjunctive therapy.  
**ACTIONS** Frisium (clobazam) is a 1,5-benzodiazepine with anticonvulsant properties. In general, the mode of anti-epileptic action of clobazam is probably largely analogous to that of the 1,4-benzodiazepines. The differences between clobazam (a 1,5-benzodiazepine) and the 1,4-benzodiazepines in terms of therapeutic efficacy and neuro-toxicity are possibly due to the variation in degree of the agonist action at the high affinity benzodiazepine receptor or to differing relative action at the high and low affinity benzodiazepine receptors. Regarding the mechanism of action, it is likely that modifications to the function of gamma-aminobutyric acid (GABA) as an important inhibitory neurotransmitter underlie the pharmacological effects of the benzodiazepines. Electro-physiologic studies have shown that benzodiazepines potentiate GABA-ergic transmission at all levels of the neuroaxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex. The changes induced by the interaction of GABA with its receptors is enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain. The oral absorption of clobazam, like that of all benzodiazepines, is fast and complete. The time to peak concentration ranges from 1 to 4 hours. The administration of food with the drug has variable effects on the rate of absorption. The drug is highly lipophilic and is rapidly distributed in fat and cerebral gray matter. Within 1 to 4 hours of administration it has accumulated in white matter and is then redistributed widely. The volume of distribution is large. Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. Clobazam forms a number of metabolites with N-desmethylclobazam being the most important. The half-life of N-desmethylclobazam is much longer (mean 42 hours; range 36-46 hours) than for clobazam (mean 18 hours; range 10-30 hours). N-desmethylclobazam reaches higher serum levels, especially with long term administration of clobazam. The half-life increases with the patient's age. The drug is about 85% protein-bound; hepatic disease may alter both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels. There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethylclobazam to clobazam efficacy. Most reports indicate there is no, or only a very weak, correlation between the clobazam dose, or blood levels, and its clinical effects. Therapeutic blood levels for clobazam are in the range of 50ng - 300ng/mL with the corresponding range for N-desmethylclobazam being from 1000 - 4000ng/mL. The serum levels at which anti-convulsant effects can be expected are not yet known but it can be assumed that the therapeutic range lies in the order of the figures given above. Since N-desmethylclobazam blood levels are 10-20 times higher than those for clobazam, and this metabolite also has anti-epileptic effects, it may be more important to the anti-epileptic efficacy of clobazam than the parent compound itself. After oral administration of <sup>14</sup>C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. Seven double-blind studies have been reported in which clobazam was given as adjunctive therapy versus placebo within an established anti-epileptic regimen; clobazam was shown to be significantly superior to placebo.  
**INDICATIONS** Frisium (clobazam) has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anti-convulsant therapy. **CONTRA-INDICATIONS** Hypersensitivity to clobazam, severe muscle weakness (myasthenia gravis) and narrow angle glaucoma. **WARNINGS** Use in the elderly: Frisium (clobazam) should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose. [See Precautions]. **Potential of drug effects:** Patients should be cautioned about the possibility of additive effects when Frisium is combined with alcohol or other drugs with central nervous system depressant effects. Patients should be advised against consumption of alcohol during treatment with Frisium. [See Precautions]. **Physical and psychological dependence:** Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer Frisium to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance. Signs and symptoms of withdrawal may follow discontinuation of use of Frisium; thus it should not be abruptly discontinued after prolonged use. [See Precautions]. **Use in pregnancy:** Frisium should not be used in the first trimester of pregnancy and thereafter only if strictly indicated. Nursing mothers in whom therapy with Frisium is indicated should cease breast-

feeding, since clobazam passes into breast milk. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If Frisium is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant. **Anterograde amnesia:** Anterograde amnesia is known to occur after administration of benzodiazepines. **Use in patients with depression or psychosis:** Frisium is not recommended for use in patients with depressive disorders or psychosis. **PRECAUTIONS Driving and Hazardous Activities:** Frisium (clobazam) possesses a mild central nervous system depressant effect, therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy. **Use in the Elderly:** Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions. **Dependence Liability:** Frisium should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, Frisium should be withdrawn gradually. **Tolerance:** Loss of part or all of the anti-convulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development. The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur. **Use in Mental and Emotional Disorders:** It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, Clobazam should not be used in patients suspected of having psychotic tendencies. **Use in Patients with Impaired Renal or Hepatic Function:** Clobazam requires dealkylation and hydroxylation before conjugation. Usual precautions should be taken if Frisium is used in patients who may have some impairment of renal or hepatic function. It is suggested that the dose in such cases be carefully titrated. In patients for whom prolonged therapy with Frisium is indicated, blood counts and liver function should be monitored periodically. **Use in Patients with Acute, Severe Respiratory Insufficiency:** In patients with acute, severe respiratory insufficiency, respiratory function should be monitored. **Laboratory Tests:** If Frisium is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable. **Drug Interactions:** Most studies of the potential interactions of clobazam with other anti-epileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur. Alcohol may also significantly increase plasma clobazam levels. **Several of the established anti-epileptic agents:** carbamazepine, diphenylhydantoin, phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethylclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenylhydantoin. **Toxicologic Studies:** In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased

incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver. (See Carcinogenicity) The relevance of these findings to man has not been established. **ADVERSE REACTIONS** From 19 published studies of Frisium (clobazam) use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects. The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%); p<0.05, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]) while other effects occurred at a less than 1% incidence. Symptoms of tiredness may sometimes appear, especially at the beginning of treatment with Frisium and when higher doses are used. Also in rare instances and usually only temporarily, the patient may experience dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, disorientation, tiredness, or a fine tremor of the fingers, but also paradoxical reactions, e.g., restlessness and irritability. After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly in elderly patients; it sometimes persisted for some length of time. Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, the drug may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. As with other drugs of this type (benzodiazepines), the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Isolated cases of skin reactions such as rashes or urticaria have been observed. **SYMPTOMS AND TREATMENT OF OVERDOSAGE Symptoms:** The cardinal manifestations are drowsiness, confusion, reduced reflexes, increasing sedation, and coma. Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and overstimulation usually when the effects of the drug begin to wear off. **Treatment:** Immediate gastric lavage may be beneficial if performed soon after ingestion of Frisium (clobazam). Given the route of excretion, [see 'ACTIONS' Section] forced diuresis by short acting 'loop' diuretic may be useful some hours post-ingestion. If respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. Respiration, pulse and blood pressure should be monitored. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of intravenous fluids started. Hypotension and central nervous system depression are managed by the usual means. **DOSE AND ADMINISTRATION** As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind. In patients with impaired liver and kidney function, Frisium (clobazam) should be used in reduced dosage. **Adults:** Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary. **Children:** In infants (<2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day. As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that Frisium be gradually reduced in dose before treatment is discontinued. **Administration:** If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night. **DOSE FORM Composition:** Frisium (clobazam) tablets, 10 mg contain clobazam as active ingredient; Lactose, USP; Starch (Corn), NF; Talc, USP; Colloidal Silicon Dioxide, NF; and Magnesium Stearate, NF. **Storage Conditions:** Frisium tablets should be stored in their original containers at room temperature, below 25°C. **Availability:** Frisium is available as white, uncoated, bevelled, round tablets of 7 mm diameter, marked with '8GL' above and below the scorebreak on the obverse and the Hoechst 'Tower and Bridge' logo on the reverse. Frisium 10 mg tablets are packaged in blisters of PVC film and aluminium foil and are distributed in packs of 30 [3x10] tablets.

Product Monograph available on request.

**References:**

1. Clobazam in the Treatment of Refractory Epilepsy - The Canadian Experience: The Canadian Clobazam Cooperative Group. In press *Epilepsia*, 1991. Data on file Hoechst Canada Inc.
2. Shorvon, S.D.: Benzodiazepines - clobazam. *Antiepileptic Drugs*, 3rd ed., 1989.

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