Ticlid®

TICLID (ticlopidine hydrochloride) 250 mg Tablets
THERAPEUTIC CLASSIFICATION Inhibitor of Platelet Function
ACTION *Ticlid (ticlopidine hydrochloride) is an inhibitor of platelet aggregation. It causes a time and dose-*dependent inhibition of platelet aggregation and release of platelet factors, as well as a prolongation of bleeding time. The drug has no significant in-vitro activity.
The exact mechanism of action is not fully characterized, but does not involve inhibition of the prostacyclin/thromboxane pathways or platelet cAMP.
Ticlid interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and *subsequent platelet-platelet interactions. The effect of Ticlid on platelet function is irreversible.*
Template bleeding time is usually prolonged by two to five-fold of baseline values with the therapeutic dose of Ticlid.
Upon discontinuation of Ticlid dosing, bleeding time and other platelet function tests return to normal within one week in the majority of patients.
The correlation between ticlopidine hydrochloride plasma levels and activity is still under investigation. Much of *the following data was obtained from older patients corresponding to the age of patients participating in clinical* trials (mean age: 63 years).
After oral administration of the therapeutic dose of Ticlid, rapid absorption occurs, with peak plasma levels occurring at approximately 2 hours after dosing. Absorption is at least 80% complete. Administration of Ticlid after meals results in an increased (20%) level of ticlopidine hydrochloride in plasma.
Steady state plasma levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 days of *dosing at 250 mg BID. The terminal elimination half-life is 4-5 days. However, inhibition of platelet aggregation is* not correlated with plasma drug levels.
Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins in a non-saturable manner.
Ticlopidine hydrochloride is metabolized extensively by the liver; no intact ticlopidine hydrochloride is detected in the urine. Unmetabolized ticlopidine hydrochloride is a minor component in plasma after a single dose, but at *steady state, ticlopidine hydrochloride is the major component.*
Impaired hepatic function resulted in higher than normal plasma levels of unchanged ticlopidine hydrochloride after single doses or after multiple doses.
Inhibition of platelet aggregation is detected within 2 days of administration with 250 mg BID. Maximum platelet aggregation inhibition is achieved 8 to 11 days following dosing with 250 mg BID.
INDICATIONS AND CLINICAL USE Ticlid (ticlopidine hydrochloride) tablets are indicated for reduction of the risk *of first or recurrent stroke for patients who have experienced at least one of the following events:* Complete Thromboembolic Stroke, Minor Stroke, Reversible Ischemic Neurological Deficit (RIND), or Transient Ischemic Attack (TIA) including Transient Monocular Blindness (TMB).
CONTRAINDICATIONS Ticlid (ticlopidine hydrochloride) is contraindicated in the following conditions: 1. Known hypersensitivity to drug or its excipients. 2. Presence of haematopoietic disorders (such as neutropenia and/or thrombocytopenia). 3. Presence of haemostatic disorder. 4. Conditions associated with active bleeding, such as bleeding peptic ulcer or intracranial bleeding. 5. Severe liver dysfunction.
WARNINGS The following warnings were developed from clinical trial experience with over 2000 patients with cerebrovascular disease who were treated with ticlopidine for as long as 5.8 years.
Neutropenia and Thrombocytopenia: About 2.4% of ticlopidine-treated patients in clinical trials developed neutropenia (defined as an absolute neutrophil count (ANC) below 1.2 x 10^9 cells/L). The incidence of severe neutropenia (ANC<0.45 x 10^9 cells/L) was 0.8%. Severe neutropenia occurs during the first 3-12 weeks of therapy, and may develop quickly over a few days. The bone marrow shows a reduction in myeloid precursors. The condition is reversible, and recovery usually occurs within 1-3 weeks after discontinuation of the drug.
In clinical trials, thrombocytopenia (defined as a platelet count of <0.8 x10^{11} cells/L) has been observed in 0.4% of ticlopidine patients. The incidence of thrombocytopenia in patients on ASA or placebo was 0.3% or 0.4% respectively. The thrombocytopenia may occur as an isolated finding or in combination with neutropenia. Thrombocytopenia occurs during the first 3-12 weeks of therapy, and recovery usually occurs after drug discontinuation.
All patients should have a white blood cell count with a differential count and platelet count performed every 2 weeks during the first 3 months of therapy. The incidence of neutropenia or thrombocytopenia after three months of therapy is not appreciably higher than the background levels observed in control groups, and continued periodic monitoring is not warranted. However, for the duration of ticlopidine therapy, any signs or symptoms suggestive of neutropenia or thrombocytopenia should be promptly investigated with complete blood counts and platelet counts.
Hemorrhagic Complications: Prolongation of bleeding time occurs in subjects treated with Ticlid. Purpura and a few cases of more serious hemorrhagic events such as hematemesis, melena, hemothorax and intracranial bleeding have been reported. Patients must be instructed to watch for signs of bleeding disorders and to report any abnormality to their physician immediately. Ticlid therapy has to be stopped by the patient if a physician is not immediately available for consultation.
Anticoagulant Drugs: Should be avoided as tolerance and safety of simultaneous administration with Ticlid has not been established.
Hepatic Abnormalities: Most patients receiving ticlopidine hydrochloride showed some increase of their alkaline phosphatase values above their baseline and in one-third the increase exceeded the upper reference range. In 6% the value was greater than twice the upper reference range. These increases in alkaline phosphatase were nonprogressive and asymptomatic. In clinical trials, two cases (0.1%) of cholestatic jaundice accompanied by elevated transaminases alkaline phosphatase, and bilirubin levels above 43µmol/L have been observed. Both patients recovered promptly upon drug discontinuation.
Pregnancy: The safety of Ticlid in pregnancy has not been established. It should not be used in pregnant patients.
Pediatric Use: Safety in children has not been studied. Do not use in pediatric patients.
PRECAUTIONS
Clinical Monitoring: All patients have to be carefully monitored for clinical signs and symptoms of adverse drug reactions (see ADVERSE REACTIONS). The signs and symptoms possibly related to neutropenia (fever, chills, sore throat, ulcerations in oral cavity), thrombocytopenia and abnormal hemostasis (prolonged or unusual bleeding, bruising, purpura, dark stool), jaundice (including dark urine, light coloured stool) and allergic reactions should be explained to the patients who should be advised to stop medication and consult their physician immediately if any of these occur.
Laboratory Monitoring: All patients should have a WBC count with differential and platelet count performed every 2 weeks during the first 3 months of therapy. Thereafter, the WBC counts need only be repeated for symptoms or signs suggestive of neutropenia. Liver function tests should be conducted during therapy with Ticlid (ticlopidine hydrochloride) in response to signs and symptoms suggestive of hepatic dysfunction.
Elective Surgery: Ticlid should be discontinued 10 to 14 days prior to elective surgery or dental extraction and bleeding time and thrombocyte count performed before the procedure if clinically indicated.
Emergency Surgery: Prolonged bleeding during surgery may be a problem in ticlopidine-treated patients. *Transfusions of fresh platelets would be expected to improve haemostasis in such patients, but there are no data* from clinical trials to confirm this expectation. There are data from clinical pharmacology trials that indicate treatment with glucocorticosteroids can normalize bleeding time in ticlopidine treated subjects, but there is no experience with ticlopidine-treated surgical patients to show that such treatment improves haemostasis.
Selection of Patients: Ticlid should be used only for the established indications (see INDICATIONS) and should not be given to patients with haematopoietic disorders, haemostatic disorders, patients suffering from conditions *associated with active bleeding (see CONTRAINDICATIONS) and patients anticipating elective surgery. In clinical* trials elderly patients tolerated the drug well, but safety in children and pregnant women has not been established.
Specific Precautions: Liver: Ticlid is contraindicated in patients with severe liver dysfunction or cholestatic jaundice. Mild increase of Alkaline Phosphatase may be seen for the duration of the treatment and is inconsequential in the majority of patients (see WARNINGS and CONTRAINDICATIONS).
Kidneys: Ticlid has been well tolerated in patients with moderately decreased renal function. In severe renal *disease, caution and close monitoring are recommended.*
Gastrointestinal System: Conditions associated with active bleeding, such as bleeding ulcers, constitute contraindication for Ticlid. Clinical judgement and monitoring of stool for occult blood are required for patients with a history of ulcerative lesions. Trauma: Ticlid should be discontinued temporarily until the danger of abnormal bleeding is eliminated. A single fatal case of intracranial bleeding following head trauma has been reported. The extent to which Ticlid may have contributed to the severity of the bleeding is unknown.
Drug Interactions: The following table outlines the agents which have been concomitantly administered with ticlopidine hydrochloride and the observed interaction if any:

AGENTS	OBSERVED INTERACTION
Acetylsalicylic acid (ASA)	Potentiation of ASA's effect on collagen-induced platelet aggregation (see WARNINGS).
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in t1/2 of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride.
Theophylline	t1/2 of theophylline increased from 8.6 to 12.2 hr along with a comparable reduction in its total plasma clearance.
Digoxin	Approximately 15% reduction in digoxin plasma levels, (little or no change in digoxin's efficacy expected).
Cimetidine	Chronic administration of cimetidine induced a 50% reduction in clearance of a single dose of ticlopidine hydrochloride.
Antacids	20% decrease in ticlopidine plasma level when administered after antacids.
Phenobarbital	No interaction reported.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, TICLID was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (however see WARNINGS) without evidence of clinically significant adverse interactions.
ADVERSE REACTIONS Most adverse effects are mild, transient and occur early in the course of treatment.
In controlled clinical trials of 1 to 5 years duration, discontinuation of Ticlid (ticlopidine hydrochloride) due to one or more adverse effects was required in 20.9% of patients. In these same trials, ASA and placebo led to discontinuation in 14.5% and 6.7% of patients respectively. The incidence rates of adverse reactions listed in the following table were derived from multicenter, controlled clinical trials comparing ticlopidine HCl, placebo, and ASA over study periods of up to 5 years. The rates are based on adverse reactions considered probably drug-related by the investigator. Adverse experiences occurring in greater than one percent of patients treated with Ticlid in controlled clinical trials are shown in the Table below.
PERCENT OF PATIENTS IN CONTROLLED STUDIES

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

* Percent of patients (in parentheses) discontinuing clinical trials due to event
The incidence of thrombocytopenia in these controlled studies was 0.4% in the Ticlid and placebo groups of patients and 0.3% in the ASA patient population.
The following rare events have been reported and their relationship to Ticlid is uncertain.
Pancytopenia, hemolytic anemia with reticulocytosis, thrombocytopenic thrombotic purpura, jaundice, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, nephrotic syndrome, myositis, and hyponatremia.
Gastrointestinal: Ticlid therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild and transient in nature and occur within 3 months of initiation of therapy. Typically, events are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued.
Hemorrhagic: Ticlid has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding, and postoperative bleeding.
Intracerebral bleeding was rare in clinical trials with Ticlid, and was no more than that seen with comparator agents (ASA, placebo).
Rash: Ticlopidine hydrochloride has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean time to onset of 11 days. If drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of more severe rashes.
Altered Laboratory Findings: Hematological: Neutropenia and rarely thrombocytopenia have been associated with Ticlid administration (see WARNINGS).
Liver: Ticlid therapy has been associated with elevations of alkaline phosphatase (See WARNINGS). Maximal changes occur within 1-4 months of therapy initiation. No further progressive increases are seen with continuous therapy. Occasionally patients developed deviations in bilirubin and SGOT.
Cholesterol: Chronic Ticlid therapy has been associated with increased serum cholesterol and triglycerides. Serum levels of HDL-C, LDL-C, VLDL-C, and triglycerides are increased 8-10% after 1-4 months of therapy. No further progressive elevations are seen with continuous therapy. The ratios of the lipoprotein subfractions are unchanged. The effect is not correlated with age, sex, alcohol use, or diabetes.
SYMPTOMS AND TREATMENT OF OVERDOSAGE One case of deliberate overdosage with Ticlid (ticlopidine hydrochloride) has been reported in a foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of Ticlid (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Based on animal studies, overdosage may result in severe gastrointestinal intolerance.
In the case of excessive bleeding after injury or surgery, standard supportive measures should be carried out if indicated, including gastric lavage, platelet transfusion and use of corticosteroids.
DOSAGE AND ADMINISTRATION The recommended dose of Ticlid (ticlopidine hydrochloride) is 250 mg twice *daily with food. Ticlid should be taken with meals to minimize gastrointestinal intolerance.*
PHARMACEUTICAL INFORMATION
(i) Drug Substance
Description: Ticlopidine hydrochloride is a white crystalline solid. It is freely soluble in water and self buffers to a pH of 3.6. It also dissolves freely in methanol, is sparingly soluble in buffer solutions above pH 6.0, methylene chloride and ethanol, and is slightly soluble in acetone.
(ii) Composition: Ticlopidine hydrochloride tablets are provided, as white film coated tablets containing ticlopidine hydrochloride, citric acid, povidone, microcrystalline cellulose, corn starch, stearic acid powder, magnesium stearate and water. The coating suspension consists of hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol. The ink for printing contains D&C yellow #10 aluminum lake and FD&C blue #1 aluminum lake.
(iii) Stability and Storage Recommendations: Store at room temperature. Ticlid tablets should be dispensed in light *resistant containers. Blister packs should not be exposed to light.*
AVAILABILITY Ticlid 250 mg tablets are oval white film coated tablets printed using green ink with Ticlid above half an arrow on one side, "250" above half an arrow on the other side. The tablets are available in 2-week Patient Starter Packs of 28 tablets (2 blisters of 14 tablets). They are also available in boxes of 56 (4 x 14) tablets and 168 (12 x 14) tablets.
For the first 3 months of therapy, only request or dispense the 14 days supply of tablets (see PRECAUTIONS).
Product Monograph available to Health Professionals on request.
REFERENCES 1. 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. Biller 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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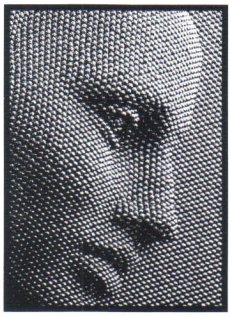

Prescribing Information

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 I: Pharmacokinetic parameters of flunarizine in healthy volunteers

	No. of Doses	Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC (ng/mL*h)	$t_{1/2\alpha}$ (h)	Clp (mL/min)	$t_{1/2\beta}$ (mean days) [range]
Single Dose Studies		5	30.5	2–4	133[a]	2.4		
		10	81.5		615[d]	2.8		
		20	117.0		1091[d]	3.6		
		30	81.6	2–6	1169[a]	5	443.7	4 [2–8]
Multiple Dose Studies	14	5	18.1[b]					
	14	10	38.8[b]					
	14	15	68.4[b]		1264[d]		301.2	[4–19]
	57	10	114.5		1678[d]			19

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 asthena 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.

REFERENCES

1. Martínez-Lage JM. Flunarizine (Sibelium) in the prophylaxis of migraine. An open, long-term, multicenter trial. *Cephalalgia* 1988; 8 (Suppl 8): 15–20. 2. Amery WK et al. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache J* 1985; 25(5): 249–54. 3. Sibelium product monograph. 4. Compendium of Pharmaceuticals and Specialties, 26th edition, 1991. 5. Todd PA; Benfield P. Flunarizine: A reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; 38(4): 481–99. 6. Borgers M et al. Selective blockade of Ca^{2+}-overload by flunarizine. *Inter Angio* 1984; 3:25–31.

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Epival*

divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Musculoskeletal: Weakness has been reported.

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

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

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

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

Other: Edema of the extremities has been reported.

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

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

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

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

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

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg; 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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PAAB MEMBER RMAC

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See page xvi

PARLODEL* (bromocriptine mesylate)

Because quality of life is the issue

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

AVAILABILITY

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

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

*Registered trademark

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Dorval Quebec H9R 4P5

See IFC

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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 β 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 averaging 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 μg/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. It is, 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 antiepileptic drug (e.g. valproic acid plus carbamazepine plus phenobarbitone and/or phenytoin) is greater than in those of women receiving a single antiepileptic. 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 antiepileptic 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. Antiepileptic 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_1 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, felodipine, 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, diltiazam, propoxyphene, viloxazine, 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 an 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 antiepileptic 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 erythrematosus-like syndrome; isolated cases - toxic epidermal necrolysis (Lyell's syndrome), photosensitivity, erythremia multiform 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 gynecomastia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine i.e. FT_4, T_4, T_3, 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, hypothermia/hyperthermia, 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 overdose, 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 Chewtabs 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 Chewtabs. **TEGRETOL Chewtabs 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 Chewtabs. **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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September, 1991

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Geigy Mississauga, Ontario L5N 2W5

PAAB CCPP G-90136

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 amines 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 paradoxica) 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. Basle Symposium, Editones 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.

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DIRECTOR OF CLINICAL NEUROPHYSIOLOGY

The Department of Internal Medicine, Faculty of Medicine, University of Manitoba, and St. Boniface General Hospital are searching for a Director of Clinical Neurophysiology. The Clinical Neurophysiology Laboratory has state-of-the art equipment and facilities. Opportunities and facilities for clinical and/or basic science research also exist. This will be a geographical full-time, contingent position at the University of Manitoba with the academic rank of either Assistant or Associate Professor, depending on qualifications.

The responsibilities would include administration of the Laboratory, interpretation of procedures, commitment in patient care, teaching and research. The proportion of time devoted to each of these activities is negotiable and experience and seniority would be taken into consideration. The candidates must have experience in Neurophysiology and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification in Neurology by the Royal College of Physicians and Surgeons of Canada is preferred. It is expected that candidates will have proven records of research ability, administrative capability and teaching experience. Salary will be commensurate with experience and qualifications.

The University of Manitoba invites applications from qualified women and men including members of visible minorities, aboriginal people and persons with disabilities. The University offers a smoke-free environment, save for specially designated areas. In accordance with Canadian Immigration requirements, this position is directed to Canadian citizens and permanent residents.

Candidates should apply in writing enclosing a Curriculum Vitae to: DR. NEELAN PILLAY, HEAD, SECTION OF NEUROLOGY, DEPARTMENT OF INTERNAL MEDICINE, ROOM F-542, HEALTH SCIENCES CENTRE, 820 SHERBROOK STREET, WINNIPEG, MANITOBA, CANADA, R3A 1R9. Closing date for receipt of applications is OCTOBER 31, 1992.

FELLOWSHIP NEUROSURGICAL ONCOLOGY

The Neurosurgery division of Memorial Sloan Kettering Cancer Center is offering a one or two year fellowship beginning July, 1993. Neurosurgeons or neurosurgeons-in-training interested in neurosurgical oncology and related research are invited to apply.

A wealth of patients with primary and metastatic tumours of the brain and spine provide a unique opportunity for experience in comprehensive management and clinical research.

Participation in a variety of basic research projects is offered and encouraged.

Reply to:

Joseph H. Galicich, M.D.
Neurosurgery Service
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10021

AN EQUAL OPPORTUNITY EMPLOYER

ACADEMIC NEUROLOGIST

The Division of Neurology, University of Toronto, is looking for an Academic Neurologist with commitment to teaching/research to be based at Women's College Hospital.

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

Applicants should be eligible for certification in Neurology by the Royal College of Physicians and surgeons of Canada.

Please forward C.V. and reference letters to:

Dr. A. Day
Physician-in-Chief, Medicine
Women's College Hospital
76 Grenville Street
Toronto, Ontario M5S 1B2
Tel: (416) 323-6127

The University of Calgary

NEUROLOGIST/MS CLINIC DIRECTOR

The University of Calgary Department of Clinical Neurosciences and the Calgary General Hospital invite applications for a full-time academic Neurologist with clinical and research experience in multiple sclerosis. The successful applicant will direct the Multiple Sclerosis Clinic at the Calgary General Hospital and the research program. Qualifications include certification in neurology and eligibility for licensure in the Province of Alberta. Rank and salary will be commensurate with qualifications and experience.

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada. The University of Calgary has an Employment Equity Program and encourages applications from all qualified candidates, including women, aboriginal people, visible minorities, and people with disabilities.

Please send a curriculum vitae and the names of three referees by August 31, 1992, to:

Dr. T.E. Feasby
Professor and Head
Department of
Clinical Neurosciences
The University of Calgary
1403 - 29 Street N.W.
Calgary, Alberta T2N 2T9

THE UNIVERSITY OF CALGARY

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HEAD OF NEUROSURGERY

The Toronto Hospital comprising the Toronto General and Toronto Western Divisions has begun a search for the Head of the Division of Neurosurgery. The Toronto Hospital has nine neurosurgeons on its full-time staff and has subspecialty expertise in areas of cerebrovascular, neurotrauma, stereotactic and functional, pain and neurooncology. The Division is located at the Toronto Western and has neurosurgical laboratories conducting research in neurooncology, cerebrovascular neurosurgery and spinal cord trauma. There is a sixteen bed Neurosurgical Intensive Care Unit, three neurosurgical operating rooms (1800 cases annually), and sixty-five neurosurgical beds on three Neurosciences Wards shared with neurology. The Division of Neurosurgery is a partner in the Toronto Hospital Neurological Centre.

Preference for this position will be given to a Canadian Neurosurgeon. All applicants should submit an introductory letter and curriculum vitae to:

Dr. Paul Walker
Surgeon-in-Chief
The Toronto Hospital
585 University Ave.
BW 1-635
Toronto, Ontario
M5G 2C4

NEUROLOGY RESIDENCY
McGILL UNIVERSITY: QUEBEC

Positions for July 1, 1993 for a three-year training program in neurology and the neurosciences leading to FRCP certification. Applicants must be Canadian graduates with two years of training in internal medicine, and currently residing outside Quebec. The core three-year program consists of 27 months of clinical training (adult and child neurology, epilepsy/EEG, neuromuscular disease/EMG), a six-month basic neurosciences research laboratory rotation and a three-month elective. The emphasis is on contemporary basic neuroscience and excellent clinical training. Apply to: Dr. Gordon S. Francis, Director, Neurology Residency Program, Montreal Neurological Institute, 3801 University Street, Montreal, Quebec H3A 2B4. Telephone (514) 398-1904.

PEDIATRIC NEUROLOGY

The Department of Pediatrics, Division of Pediatric Neurology, at McMaster University, Hamilton, Ontario is seeking a Locum in Child Neurology for a period of approximately 7 months beginning in September 1992. Certification in neurology or pediatrics by the Royal College of Physicians and Surgeons of Canada or equivalent experience in pediatric neurology will be required. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens or permanent residents. Please submit enquiries and curriculum vitae to:

Dr. G.M. Ronen, M.D.
Head, Division of Pediatric Neurology
Department of Pediatrics
McMaster University
1200 Main Street West
Hamilton, Ontario
Phone: (416) 521-2100 Ext. 5235
Fax: (416) 521-1703

University of Toronto

CENTRE FOR RESEARCH IN NEURODEGENERATIVE DISEASES

Applications are invited for two positions in a recently established neurodegenerative disease research centre with emphasis on Alzheimer's disease, Ph.D.s or M.D.s at the Assistant, Associate or Full Professor level are sought to join this team of 7 P.I.s. Candidates must have expertise in one of the following areas of neurobiology: transgenic models, biochemically oriented molecular biology, protein structure, or gene regulation. Start up funds provided; successful candidates must initiate independent and original research programs.

The University of Toronto encourages applications from qualified men and women, members of visible minorities, aboriginal peoples and persons with disabilities. In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents.

Send curriculum vitae, a research statement and three letters of reference prior to September 1, 1992, to Dr. D.R. McLachlan, Centre for Research in Neurodegenerative Diseases, Tanz Neuroscience Building, 6 Queen's Park Cr. W., Toronto, Ontario, Canada M5S 1A8.

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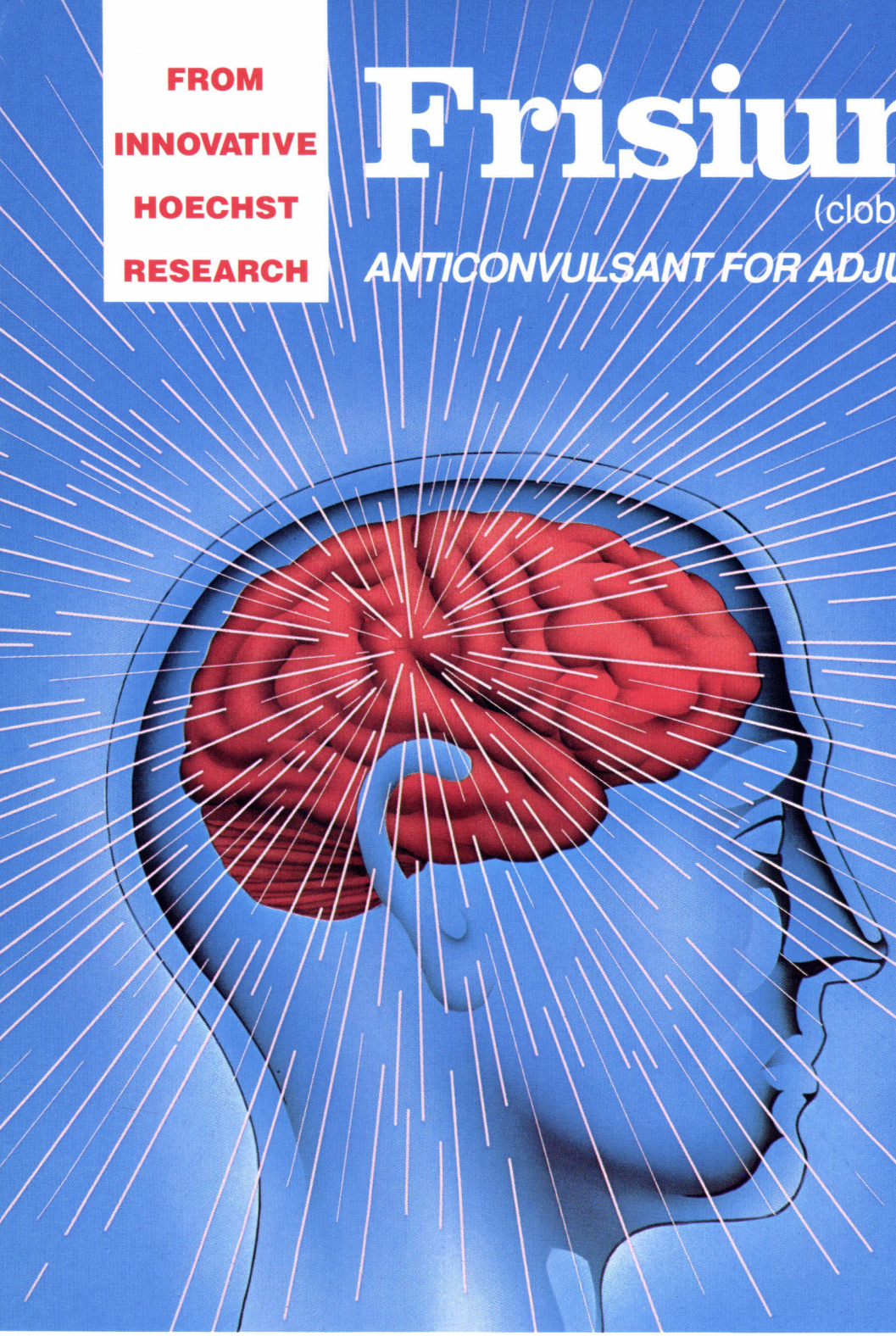

EFFICACY

- **Frisium** is efficacious in all seizure types in both pediatric and adult patients.[1]
- **Frisium** achieves complete control in up to 30% of refractory patients depending on seizure type.[1]

SAFETY

- Adverse events are generally mild and transient.[2]
- Clinically significant drug interactions are uncommon.
- Impairment of alertness is less pronounced with **Frisium** than with other benzodiazepines.*

DOSAGE

- Daily doses up to 30 mg may be taken as a single dose at bedtime.

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Unfortunately, some antiepileptic drugs can suppress more than seizures.

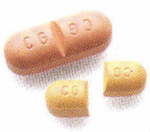
Some antiepileptic drugs such as phenytoin can impair a patient's cognitive abilities.[1,2,3,4]

In contrast, Tegretol® CR (controlled release carbamazepine) has little impact on cognitive function while providing excellent seizure control.[1,2,3,4]

Tegretol CR delivers more consistent blood levels than conventional Tegretol. Therefore, it can reduce the frequency of intermittent side-effects and offers a more stable pattern of cognitive functioning.[5,6]

When initiating therapy, or switching therapy as medically appropriate, consider Tegretol CR. It comes in easy-to-break 200 mg and 400 mg tablets for dosage flexibility and with a convenient B.I.D. dosing schedule to enhance patient compliance.

Tegretol CR. Because the last thing an antiepileptic drug should affect is potential.



TEGRETOL® CR.

Helping epilepsy patients reach their full potential.

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For prescribing information see pages xxi and xxii