

SINEMET[®] CR

(levodopa/carbidopa) CONTROLLED-RELEASE

200/50
100/25

Controlled-Release Tablets Antiparkinson Agent

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

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

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

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

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

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

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

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

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

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

SINEMET[®] CR should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other drugs: Although specific interaction studies were not performed with other concomitant drugs, in clinical trials of SINEMET[®] CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, thiazides, digoxin, H₂ antagonists, salicylates and other nonsteroidal anti-inflammatory drugs. SINEMET[®] CR was also used with other antiparkinson agents (see DOSAGE AND ADMINISTRATION).

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

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

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

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

Systemic: Body as a whole: Chest pain 1.7%, Fatigue 0.9%, Weight loss 0.8%.
Cardiovascular: Orthostatic hypotension 0.8%, Palpitation 0.8%, Hypotension 0.5%.

Nervous System / Psychiatric: Insomnia 1.7%, Falling 1.6%, On-off phenomenon 1.2%, Paresthesia 0.9%, Disorientation 0.8%, Anxiety disorders 0.8%, Decreased mental acuity 0.7%, Extrapyramidal disorder 0.7%, Gait abnormalities 0.7%, Agitation 0.5%, Memory impairment 0.5%.
Gastrointestinal: Anorexia 1.9%, Constipation 1.5%, Vomiting 1.3%, Diarrhea 1.2%, Gastrointestinal pain 0.9%, Dyspepsia 0.8%.
Musculoskeletal: Muscle cramps 0.9%.

Respiratory: Dyspnea 1.6%.
Special Senses: Blurred vision 1.1%.

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

Nervous System: Ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome.
Psychiatric: Sleepiness, euphoria, paranoid ideation and psychotic episodes, and dementia.

Cardiovascular: Arrhythmias, non-specific ECG changes, flushing, phlebitis.
Gastrointestinal: Bitter taste, sialorrhea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.
Integumentary: Increased sweating, dark sweat, rash, hair loss.

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

Special Senses: Diplopia, dilated pupils, oculo-crisis.
Hematologic: Leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

Miscellaneous: Weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, hypertension, neuroleptic malignant syndrome, malignant melanoma (see CONTRAINDICATIONS).

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

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

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

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

Symptoms and Treatment of Overdosage: Management of acute overdosage with SINEMET[®] CR (levodopa and carbidopa) is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET[®] CR.

Electrocardiographic monitoring should be instituted and the patient observed carefully for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET[®] CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Dosage and Administration: SINEMET[®] CR (levodopa and carbidopa) Tablets contain a 4:1 ratio of levodopa to carbidopa. SINEMET[®] CR 200/50 contains levodopa 200 mg/carbidopa 50 mg per tablet. SINEMET[®] CR 100/25 contains levodopa 100 mg/carbidopa 25 mg per tablet. The daily dosage of SINEMET[®] CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

SINEMET[®] CR 200/50 may be administered as whole or as half tablets. SINEMET[®] CR 100/25 should only be administered as whole tablets. To maintain the controlled-release properties of the product, tablets should not be chewed or crushed.

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

Initial Dosage and Titration for Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations: Dosage with SINEMET[®] CR 200/50 should be substituted at an amount that eventually provides approximately 10 to 30 percent more levodopa per day. The interval between doses should be prolonged by 30 to 50 percent. Initially, patients should receive SINEMET[®] CR 200/50 at a dosage that provides the same amount of levodopa, but with a longer dosing interval. Depending on clinical response, the dosage may be increased.

A guide for the initiation of treatment with SINEMET[®] CR 200/50 is shown in the following table:

Guideline for Initial Conversion
from SINEMET[®] to SINEMET[®] CR 200/50

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

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

SINEMET[®] CR 100/25 is available to facilitate titration when 100 mg steps are required and as an alternative to the half tablet of SINEMET[®] CR 200/50.

Initial Dosage for Patients Currently Treated with Levodopa Alone: Levodopa must be discontinued at least eight hours before therapy with SINEMET[®] CR 200/50 is started. SINEMET[®] CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET[®] CR 200/50 two times daily.

Patients Without Prior Levodopa Therapy: Experience with SINEMET[®] CR is limited in the *de novo* parkinsonian patients.

SINEMET[®] CR 100/25 may be used in early stage patients who have not had prior levodopa therapy or to facilitate titration when necessary in patients receiving SINEMET[®] CR 200/50. The initial recommended dose is 1 tablet of SINEMET[®] CR 100/25 twice daily. For patients who require more levodopa, a daily dose of 1 to 4 tablets of SINEMET[®] CR 100/25 twice a day is generally well-tolerated.

When appropriate, levodopa therapy may also be initiated with SINEMET[®] CR 200/50. The initial recommended dose in patients with mild to moderate disease is 1 tablet of SINEMET[®] CR 200/50 two times daily. Initial dosages should not exceed 600 mg per day of levodopa or be given at intervals of less than 6 hours.

If the divided doses of SINEMET® CR 200/50 are not equal, it is recommended that the smaller doses be given at the end of the day.

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

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

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

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

Pharmaceutical Information

I. Drug Substance

Proper name: levodopa and carbidopa

Chemical name:

Levodopa
(-)-3-(3,4-Dihydroxyphenyl)-L-alanine.

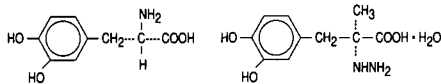
Carbidopa
(-)-L-α-Hydrazino-3,4-dihydroxy-α-methyl-hydrocinamic acid monohydrate.

Empirical formula:

C₉H₁₁NO₄

C₁₀H₁₄N₂O₄ • H₂O

Structural formula:



Molecular weight:

197.2

244.3

Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3

Description:

Levodopa, an aromatic amino acid, is a white crystalline compound, slightly soluble in water.

Carbidopa, an inhibitor of aromatic amino acid decarboxylase is a white, crystalline compound, slightly soluble in water.

II. Composition

SINEMET® CR is a controlled-release formulation of levodopa and carbidopa, in a ratio of 4:1. The tablet contains a polymer-based drug delivery system which controls the release of levodopa and carbidopa as it slowly erodes. Excipients include hydroxypropyl cellulose, NF and magnesium stearate, NF. SINEMET® CR 100/25 Tablets contain red ferric oxide, NF. SINEMET® CR 200/50 Tablets contain red ferric oxide, NF and D&C Yellow No. 10.

III. Storage Recommendations

Store between 15°C (59°F) and 30°C (86°F). Protect from sunlight.

Availability of Dosage Forms: No. 2042 - SINEMET® CR 100/25 is a pink-colored, oval-shaped, biconvex, compressed tablet, engraved SINEMET CR on one side and 601 on the other. Available in bottles of 100.

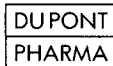
No. 2041 - SINEMET® CR is peach-colored, oval-shaped, biconvex, scored compressed tablet, engraved SINEMET CR on one side and 521/521 on the other. Available in bottles of 100.

Product Monograph Available on Request

(384-a.4.93)

04-94-SCR-93-CDN-0040-JA

2655 North Sheridan Way
Mississauga, Ontario
L5K 2P8



P A A B

See page xi.

IN EPILEPSY, ADD

Frisium® 10 mg
(clobazam)
TO ACHIEVE SEIZURE CONTROL

Frisium (clobazam) Tablets 10 mg.

THERAPEUTIC CLASSIFICATION Anticonvulsant for adjunctive therapy. **INDICATIONS** Frisium (clobazam) has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anti-convulsant therapy. **CONTRAINDICATIONS** Hypersensitivity to clobazam, severe muscle weakness (myasthenia gravis) and narrow angle glaucoma. **WARNINGS Use in the elderly:** Frisium (clobazam) should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose. [See Precautions]. **Potential of drug effects:** Patients should be cautioned about the possibility of additive effects when Frisium is combined with alcohol or other drugs with central nervous system depressant effects. Patients should be advised against consumption of alcohol during treatment with Frisium. [See Precautions]. **Physical and psychological dependence:** Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer Frisium to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance. Signs and symptoms of withdrawal may follow discontinuation of use of Frisium; thus it should not be abruptly discontinued after prolonged use. [See Precautions]. **Use in pregnancy:** Frisium should not be used in the first trimester of pregnancy and thereafter only if strictly indicated. Nursing mothers in whom therapy with Frisium is indicated should cease breast-feeding, since clobazam passes into breast milk. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If Frisium is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant. **Anterograde amnesia:** Anterograde amnesia is known to occur after administration of benzodiazepines. **Use in patients with depression or psychosis:** Frisium is not recommended for use in patients with depressive disorders or psychosis. **PRECAUTIONS Driving and Hazardous Activities:** Frisium (clobazam) possesses a mild central nervous system depressant effect, therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy. **Use in the Elderly:** Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions. **Dependence Liability:** Frisium should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, Frisium should be withdrawn gradually. **Tolerance:** Loss of part or all of the anti-convulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development. The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur. **Use in Mental and Emotional Disorders:** It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, Clobazam should not be used in patients suspected of having psychotic tendencies. **Use in Patients with Impaired Renal or Hepatic Function:** Clobazam requires dealkylation and hydroxylation before conjugation. Usual precautions should be taken if Frisium is used in patients who may have some impairment of renal or hepatic function. It is suggested that the dose in such cases be carefully titrated. In patients for whom prolonged

therapy with Frisium is indicated, blood counts and liver function should be monitored periodically. **Use in Patients with Acute, Severe Respiratory Insufficiency:** In patients with acute, severe respiratory insufficiency, respiratory function should be monitored. **Laboratory Tests:** If Frisium is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable. **Drug Interactions:** Most studies of the potential interactions of clobazam with other anti-epileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur. Alcohol may also significantly increase plasma clobazam levels. **Several of the established anti-epileptic agents:** carbamazepine, diphenylhydantoin, phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethyloclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenylhydantoin. **Toxicologic Studies:** In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver. The relevance of these findings to man has not been established. **ADVERSE REACTIONS** From 19 published studies of Frisium (clobazam) use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects. The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%); p < 0.05, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]) while other effects occurred at a less than 1% incidence. Symptoms of tiredness may sometimes appear, especially at the beginning of treatment with Frisium and when higher doses are used. Also in rare instances and usually only temporarily, the patient may experience dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, disorientation, tiredness, or a fine tremor of the fingers, but also paradoxical reactions, e.g., restlessness and irritability. After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly in elderly patients; it sometimes persisted for some length of time. Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, the drug may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. As with other drugs of this type (benzodiazepines), the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Isolated cases of skin reactions such as rashes or urticaria have been observed. **DOSE AND ADMINISTRATION** As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind. In patients with impaired liver and kidney function, Frisium (clobazam) should be used in reduced dosage. **Adults:** Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary. **Children:** In infants (< 2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day. As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that Frisium be gradually reduced in dose before treatment is discontinued. **Administration:** If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night. **AVAILABILITY** Frisium is available as white, uncoated, bevelled, round tablets of 7 mm diameter, marked with 'BGL' above and below the scorebreak on the obverse and the Hoechst 'Tower and Bridge' logo on the reverse. Frisium 10 mg tablets are packaged in blisters of PVC film and aluminium foil and are distributed in packs of 30 [3x10] tablets. Product Monograph available on request.

Reference: 1. Clobazam in the Treatment of Refractory Epilepsy - The Canadian Experience. A Retrospective Study, Canadian Clobazam Cooperative Group: Epilepsia, 1990;1-10.

FRI 2698/9053E



Hoechst and ®, Reg. Trademarks of Hoechst AG, Germany
Hoechst Canada Inc., Montreal H4R 2E8

See pages ibc, iii.



Intermediate 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
Antimanic

INDICATIONS A. Management of psychomotor (temporal lobe) epilepsy. As an adjunct in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when combined with other antiepileptic agents.

As an alternative in patients with generalized tonic-clonic seizures and marked side effects or who fail to respond to other anticonvulsant drugs.

Ineffective for controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent generalization of epileptic discharge. Exacerbation of seizures may occur in patients with atypical absences.

B. Symptomatic relief of pain of true or primary trigeminal neuralgia (tic douloureux). Not for prophylactic use. Glossopharyngeal neuralgia has been relieved in some patients. Other measures must be considered for patients failing to respond or who are sensitive to TEGRETOL.

C. Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders: may be used as monotherapy or adjunct to lithium in patients who are resistant to or are intolerant of conventional antimanic. Possibly an alternative to neuroleptics in such patients. Patients with severe mania, dysphoric mania or rapid cycling who are non-responsive to lithium may respond positively to carbamazepine. Recommendations are based on extensive clinical experience and some comparative trials.

CONTRAINDICATIONS History of hepatic disease, acute intermittent porphyria or serious blood disorder, in patients with AV heart block (see Precautions), hypersensitivity to carbamazepine or to tricyclic compounds, or their analogues or metabolites.

Do not give with, immediately before or immediately after treatment with monoamine oxidase inhibitors. There should be as long a drug free interval as the clinical condition allows, in no case less than 14 days. Then TEGRETOL dosage should be low initially, increased very gradually.

WARNINGS Although reported infrequently, serious adverse effects have been observed during 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 also reported. It is important that TEGRETOL be used carefully and close clinical and frequent laboratory supervision be maintained throughout treatment to detect signs and symptoms of possible blood dyscrasia, as early as possible. Discontinue TEGRETOL 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's syndrome, withdraw TEGRETOL at once. Long-term toxicity studies in rats indicated a potential carcinogenic risk. Weigh possible risk of TEGRETOL against potential benefits before prescribing.

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 offspring of women treated with more than one antiepileptic drug is greater than in those receiving single antiepileptic. Minimum effective doses should be given and plasma levels monitored.

If woman receiving TEGRETOL becomes pregnant, or if the problem of initiating TEGRETOL arises during pregnancy, weigh the drug's potential benefits against its hazards, particularly during the first 3 months of pregnancy. Do not discontinue TEGRETOL or withhold from patients if required to prevent major seizures because of the risks posed, to both mother and fetus, by status epilepticus with attendant hypoxia.

Possibility that carbamazepine, like all major antiepileptic drugs, increases the risk of malformations has been reported. 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, which may contribute to increased incidence of birth defects in offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy.

Vitamin K₁ administration to mother during last weeks of pregnancy, and to newborn, has been recommended to prevent neonatal bleeding disorders.

Carbamazepine passes into breast milk in concentrations of

about 25-60% of the plasma level. No reports available on long-term effect of breast feeding. Weigh benefits of breast feeding against possible risks to infant. Observe infant for possible adverse reactions, e.g., somnolence, should mother taking carbamazepine nurse.

A severe hypersensitivity skin reaction in a breast-fed baby has been reported.

Reliability of oral contraceptives may be adversely affected by carbamazepine (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS Clinical Monitoring of Adverse Reactions: Prescribe TEGRETOL only after a critical risk-benefit appraisal in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with TEGRETOL. Maintain careful clinical and laboratory supervision throughout treatment. Should any signs or symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, discontinue TEGRETOL immediately until case is carefully reassessed.

(a) **Bone marrow function:** Carry out complete blood counts, including platelets and possibly reticulocytes and serum iron, before treatment is instituted. Suggested guidelines for monitoring are weekly for the first month, monthly for the next 5 months, thereafter 2-4 times/year.

If definitely low or decreased white blood cell or platelet counts are observed during treatment, patient and complete blood count should be monitored closely. Non-progressive fluctuating asymptomatic leucopenia encountered, does not generally call for TEGRETOL withdrawal. However, treatment should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g. fever or sore throat, which could indicate onset of significant bone marrow depression.

Because onset of potentially serious blood dyscrasias may be rapid, patients should be made aware of early toxic signs and symptoms of potential hematological problem, and symptoms of dermatological or hepatic reactions. If reactions, e.g. fever, sore throat, rash, ulcers in mouth, easy bruising, petechial or purpuric hemorrhage appear, advise patient to consult his/her physician immediately.

(b) **Hepatic function:** Baseline and periodic evaluations of hepatic function must be performed, particularly in elderly patients and those with history of liver disease. Withdraw TEGRETOL immediately in cases of aggravated liver dysfunction or active liver disease.

(c) **Kidney function:** Perform pretreatment and periodic complete urinalysis and BUN determinations.

(d) **Ophthalmic examinations:** Carbamazepine has been associated with pathological eye changes. Periodic eye examinations, including slit-lamp funduscopy and tonometry recommended.

(e) **Plasma levels:** Although correlations between dosage and plasma levels, 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; pregnancy; when treating children or adolescents; suspected absorption disorders; suspected toxicity, especially where more than one drug is used (see "Interactions").

Increased Seizure Frequency: Use TEGRETOL with caution in patients with mixed seizure disorder that includes atypical absence seizures, since use has been associated with increased frequency of generalized convulsions. In case of exacerbation of seizures, discontinue TEGRETOL.

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 dosage decrease. However, patient should be kept under close surveillance because of 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. Follow such patients closely while on the drug.

Occurrence of Behavioural Disorders: Because it is closely related to other tricyclic drugs, there is a possibility that carbamazepine might activate latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Exercise caution in alcoholics.

Use in Patients with Cardiovascular Disorders: Use TEGRETOL cautiously in patients with history of coronary artery disease, organic heart disease, or congestive failure. If defective conductive system suspected, perform an ECG before administering TEGRETOL, to exclude patients with atrioventricular block.

Driving and Operating Hazardous Machinery: Because dizziness and drowsiness are possible side effects of TEGRETOL, warn patients about possible hazards of operating machinery or driving automobiles.

Drug Interactions: Induction of hepatic enzymes in response to carbamazepine may diminish or abolish activity of certain drugs also metabolized in the liver. Dosage of the following drugs may have to be adjusted: 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 reported to be both raised and lowered by carbamazepine, and mephenytoin plasma levels reported to increase in rare instances.

The following drugs have been shown to raise plasma carbamazepine levels: erythromycin, troleandomycin, possibly josamycin, isoniazid, verapamil, diltiazem, 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), adjust TEGRETOL dosage accordingly and monitor the blood levels.

Plasma levels of carbamazepine may be reduced by phenobarbitone, phenytoin, primidone, progabide, or theophylline, and possibly by clonazepam. Alternatively, valproic acid, valpromide, and primidone have been reported to raise plasma levels of pharmacologically active metabolite, carbamazepine-10, 11 epoxide. TEGRETOL dose may consequently require adjustment.

Combined use with lithium, metoclopramide, or haloperidol, may increase risk of neurotoxic side effects (even in presence of "therapeutic plasma levels").

Concomitant use with isoniazid 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.

TEGRETOL may antagonize 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 reported to alter the bioavailability and/or clearance of carbamazepine and its active 10, 11-epoxide; carbamazepine plasma levels should be monitored.

Carbamazepine, may reduce tolerance to alcohol; advisable to abstain from alcohol consumption during treatment.

TEGRETOL should not be administered in conjunction with MAO inhibitor. (See CONTRAINDICATIONS).

ADVERSE REACTIONS Reactions most frequently reported are CNS (e.g. drowsiness, headache, unsteadiness on feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. These reactions usually occur only during the initial phase of therapy, if 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 low dosage.

Occurrence of CNS adverse reactions may be manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor plasma levels and possibly lower daily dose and/or divide it into 3-4 fractional doses.

More serious adverse reactions observed are hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy. If treatment is to be withdrawn abruptly, effect the change-over to another antiepileptic under cover of diazepam.

Adverse reactions 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 few instances, deaths occurred.

Hepatic: Frequent - elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant; occasional - elevated alkaline phosphatase; rarely - transaminases; rare - jaundice, hepatitis of cholestatic, parenchymal, hepatocellular, or mixed type; isolated cases - granulomatous hepatitis.

Dermatologic: Occasional to frequent - skin sensitivity reactions and rashes, erythematous rashes, urticaria; rare - exfoliative dermatitis and erythroderma, Steven-Johnson syndrome, systemic lupus erythematosus-like syndrome; isolated cases - toxic epidermal necrolysis (Lyell's syndrome), photosensitivity, erythema multiforme and nodosum, skin pigmentation changes, pruritus, purpura, acne, diaphoresis, alopecia and neurodermatitis.

Neurologic: Frequent - vertigo, somnolence, ataxia and fatigue. Occasionally - an increase in motor seizures (see INDICATIONS), headache, diplopia, nystagmus, accommodation disorders (e.g. blurred vision); rare - abnormal involuntary disorders (e.g. tremor, asterix, orofacial dyskinesia, choreoathetosis disorders, dystonia, tics); isolated cases - oculomotor disturbances, speech disorders (e.g. dysarthria or slurred speech), peripheral neuritis, paraesthesias. 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, leading in isolated cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities. Isolated cases of gynecostasia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine, i.e., FT₄, T₄, T₃, 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:** 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 (slow/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.

Observe vital signs and administer symptomatic treatment 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 hyperonus 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 ECG be monitored, particularly in children, to detect cardiac arrhythmias or conduction defects. Charcoal hemoperfusion has been recommended. Forced diuresis, hemodialysis, and peritoneal dialysis 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): Low initial daily dosage of TEGRETOL (carbamazepine) with a gradual increase in dosage is advised. Adjust dosage to the needs of the individual patient.

TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals when possible.

Controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, half a tablet) should be swallowed unchewed with a little liquid during or after a meal. Controlled release tablets should be prescribed as a b.i.d. dosage. If necessary, 3 divided doses may be prescribed.

Adults and Children Over 12 Years: Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. Initial dosage is progressively increased, in divided doses, until best response is obtained. 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, reduce dosage very gradually until reaching minimum effective dose.

Children 6-12 Years: Initially, 100 mg in divided doses on first day. Increase gradually by adding 100 mg/day until best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, reduce dosage very gradually until reaching minimum effective dose.

Use in Trigeminal Neuralgia: Initial daily dosage 200 mg taken in 2 doses of 100 mg is recommended. Total daily dosage can be increased by 200 mg/day until relief of pain is obtained, usually achieved at dosage 200-800 mg daily; occasionally up to 1200 mg/day necessary. As soon as relief of pain has been obtained and maintained, attempt progressive reduction in dosage until reaching minimal effective dosage. 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 on individual clinical course.

Prophylactic use in trigeminal neuralgia is not recommended. **Use in Mania and Bipolar (Manic Depressive) Disorders:** Low initial dosage of 200-400 mg/day, in divided doses, higher starting doses of 400-600 mg/day may be used in acute mania. May be gradually increased until symptomatology is controlled or a total daily dose of 1600 mg. Adjust dosage increments for optimal tolerability. Usual dose is 400-1200 mg/day in divided doses. For maintenance, continue with doses used to achieve optimal acute responses and tolerability. In combination with lithium, neuroleptics: initially a low dosage of 100-200 mg/day; gradually increase. Daily dose > 800 mg is rarely required when given in combination with neuroleptics, lithium or other psychotropics, e.g., benzodiazepines. Plasma levels are probably not helpful for guidance in bipolar disorders.

AVAILABILITY TEGRETOL Tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Protect from heat (store below 30°C) and humidity. Bottles of 100/500. **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 contains 100 mg carbamazepine. Protect from heat (store below 30°C), light and humidity. Bottles of 100. **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 contains 200 mg carbamazepine. Protect from heat (store below 30°C), light and humidity. Bottles of 100. **TEGRETOL CR 200 mg:** Beige-orange, oval, slightly biconvex tablet, engraved CG on one side and HC on the other. Fully bisected on both sides. Each contains 200 mg carbamazepine. Protect from heat (store below 25°C) and humidity. Bottles of 100. **TEGRETOL CR 400 mg:** Brownish-orange, oval, slightly biconvex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully bisected on both sides. Each contains 400 mg carbamazepine. Protect from heat (store below 25°C) and humidity. Bottles of 100. TEGRETOL is available to patients only by prescription.

Product Monograph available on request. January 4, 1993

REFERENCES

- Smith DB, et al: Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia* 1987; 28(Suppl 3): 550-558.
- Dooley JM: Seizures in childhood. *Medicine North America* 1989; 4th series 2: 163-172.
- Aldenkamp AP, et al: Controlled release carbamazepine: cognitive side effects in patients with epilepsy. *Epilepsia* 1987; 28(5): 507-514.
- Canger R, et al: Conventional vs controlled-release carbamazepine; a multicentre, double-blind, cross-over study. *Acta Neurol Scand* 1990; 82: 9-13.

See pages obc, ix.

Geigy

Mississauga, Ontario L5N 2W5
or Dorval, Quebec H9S 1B1

PAAB
CCPP

CIBA-GEIGY

Award for Excellence in Neurological Science

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

A cash prize of \$2500 will be announced at the annual meeting of the Canadian Congress of Neurological Sciences in June. Articles published in Volume 20 will be adjudicated by the editorial board for the 1993 award.

Copies of articles from this publication are now available from the UMI Article Clearinghouse.

Yes! I would like to know more about UMI Article Clearinghouse. I am interested in electronic ordering through the following system(s):

- DIALOG/Dialorder ITT Dialcom
 OnTyme OCLC ILL Subsystem

Other (please specify) _____

I am interested in sending my order by mail.

Please send me your current catalog and user instructions for the system(s) I checked above.

Name _____

Title _____

Institution/Company _____

Department _____

Address _____

City _____ State _____ Zip _____

Phone (_____) _____

UMI Article Clearinghouse

Mail to: University Microfilms International
300 North Zeeb Road, Box 91 Ann Arbor, MI 48106

ELDEPRYL[®]

selegiline hydrochloride

FIRST LINE



Rx Summary

Antiparkinson Agent

Indications and clinical use:

As an adjunct to levodopa (with or without a decarboxylase inhibitor) in the management of the signs and symptoms of Parkinson's disease.

In newly diagnosed patients before symptoms begin to affect the patient's social or professional life, at which time more efficacious treatment becomes necessary.

Contraindications:

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

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

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

Warnings to patients:

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

Precautions:

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

NURSING MOTHERS: It is not known whether Eldepryl is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

PEDIATRIC USE: The effects of Eldepryl in children under 18 have not been evaluated.

Laboratory Tests:

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

Drug Interactions:

The occurrence of stupor, muscular rigidity, severe agitation and elevated temperature has been reported in a man receiving selegiline and meperidine, as well as other medications. These symptoms were resolved over days when the combination was discontinued. This case is typical of the interaction of meperidine and MAOIs. Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of ELDEPRYL and other drugs have been reported. It is also prudent to avoid the combination of ELDEPRYL and fluoxetine (Prozac).

Use during Pregnancy:

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

Adverse reactions:

A) IN COMBINATION WITH LEVODOPA

THE SIDE EFFECTS OF ELDEPRYL ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. ELDEPRYL MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA, THEREFORE ADJUSTMENT OF THE DOSAGE OF LEVODOPA MAY BE REQUIRED. ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS/CONFUSION, PARTICULARLY VISUAL HALLUCINATIONS.

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

B) IN MONOTHERAPY

The incidence of adverse reactions occurring in trials using Eldepryl as monotherapy has not been fully reported to date. Serious adverse reactions include depression, chest pain, myopathy and diarrhea. Other reported adverse reactions include insomnia, headache, nausea, dizziness and vertigo.

In prospective clinical trials, the following adverse effects (listed in decreasing order of frequency), led to the discontinuation of Eldepryl: Nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased aknetic involuntary movements, agitation, arrhythmia, bradykinesia chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only rarely as a cause of discontinuation

of treatment include anxiety, drowsiness/lethargy, nervousness, dystonia, increased episodes of freezing, increased tremor, weakness, excessive perspiration, constipation, weight loss, burning lips/mouth, ankle edema, gastrointestinal bleeding and hair loss.

Dosage:

The recommended dosage of Eldepryl as monotherapy in newly diagnosed patients, or as adjunct to levodopa (usually with a decarboxylase inhibitor) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. When ELDEPRYL adjunctive therapy is added to the existing levodopa therapeutic regime, a reduction, usually of 10 to 30% in the dose of levodopa (in some instances a reduction in the dose of Eldepryl to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects. Doses higher than 10 mg per day should not be used. There is no evidence that additional benefit will be obtained from the administration of higher doses. Furthermore, higher doses will result in a loss of selectivity of Eldepryl towards MAO-B with an increase in the inhibition of type MAO-A.

There is an increased risk of adverse reactions with higher doses as well as an increased risk of hypertensive episode ("cheese reaction")

Supplied:

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

References:

1. The Parkinson Study Group. Effect of Deprenyl on the Progression of Disability in Early Parkinson's Disease. *New Eng Journ* 321, 1364-1371, November 1989.
2. Eldepryl (selegiline hydrochloride) Product Monograph, December 1990.
3. Myllyla VV, Sotaniemi KA, Vuorinen JA, Heinonen EH. Selegiline as initial treatment in de novo parkinsonian patients. *Neurology* 1992; 42, 339-343.
4. Tetrud JW, Langston JW. The Effect of Deprenyl (Selegiline) on the Natural History of Parkinson's Disease. *Science*, August 1989, vol. 245, 519-522.
5. Myllyla VV, Sotaniemi KA, Vuorinen J, Heinonen EH. Selegiline (deprenyl) as primary treatment in Parkinson's disease. *Selegiline therapy in early Parkinson's disease*. July 1990, 19-24.
6. Langston JW in Lees A. *Deprenyl in Parkinson's Disease: Guidelines for Clinicians*. North American Round Table Series, No. 1, 1988, 1-26.
7. DuVoisin RC in Lees A. *Deprenyl in Parkinson's Disease: Guidelines for Clinicians*. North American Round Table Series, No. 1, 1988, 1-26.

Product Monograph available upon request.

PAAB



378 Roncesvalles Ave., Toronto, Ontario TEL: (416) 537-4372

See page vii.

Region 2 Hospital Corporation Neurosurgeon - Saint John Regional Hospital

The Saint John Regional Hospital, Saint John, New Brunswick, a teaching hospital affiliated with Dalhousie University Faculty of Medicine is currently seeking a Neurosurgeon to join two others providing a tertiary level Neurosurgery program to the Western half of the Province of New Brunswick. The Neurosurgical program is a clinical one, encompassing general and pediatric Neurosurgery, and including spinal and micro Neurosurgery.

The Saint John Regional Hospital is an 800-bed accredited tertiary facility within the Region 2 Hospital Corporation. It is a provincial referral centre for several services such as Neurosurgery, Cardiac Surgery, Interventional Cardiology, Paediatric Oncology, burns and multiple trauma. The Saint John Regional Hospital has a proven track record of dynamic leadership and sound management with an emphasis on planning. A medical information system, fully integrated in all departments, has been operational since 1981.

Saint John serves a population of 125,000 and is Canada's first incorporated city. The beautiful St. John and Kennebecasis Rivers comprise the city's waterways and offer excellent conditions for boating and other outdoor activities. It is a great place to raise a family!

Successful candidates should be certified by the Royal College of Physicians and Surgeons of Canada or eligible for such certification.

Interested candidates, please contact the undersigned:

Brian Wheelock, MD, FRCS
Head, Department of Neurosurgery
P.O. Box 2100
Saint John, NB
E2L 4L2

The Department of Pathology of the Faculty of Medicine, University of Manitoba and, the Health Sciences Centre, Winnipeg, invite applications for a contingent, geographical full-time Neuropathologist at the Health Sciences Centre.

The Section of Neuropathology provides a full range of diagnostic services to the Health Sciences Centre and the Children's Hospital.

Candidates should be research oriented and have extensive experience in basic laboratory neuropathology/neuroscience with demonstrated investigative capability, particularly in the area of astrocyte biology. Some experience in molecular technology is highly desirable. Certification (Fellowship) in Neuropathology by the Royal College of Physicians and Surgeons of Canada is essential and candidates must be eligible for registration with the College of Physicians and Surgeons of Manitoba.

Salary and academic rank will be commensurate with experience and qualifications. The University of Manitoba encourages applications from qualified women and men, including members of visible minorities, Aboriginal peoples, and persons with disabilities. The University provides a smoke-free work environment, save for specifically designated areas. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents.

Interested applicants should apply in writing, enclosing a Curriculum Vitae with the names and addresses of three referees to:

Dr. William C. Halliday
Section Head, Neuropathology &
Acting Head, Department of Pathology,
University of Manitoba & Health Sciences Centre
c/o Health Sciences Centre
820 Sherbrook Street
Winnipeg, Manitoba, Canada R3A 1R9
Ph: (204) 787-2039
Fax: (204) 787-4942

Academic Neurologist – Ontario

Victoria Hospital Corporation, London, Ontario, an equal opportunity employer and an affiliated teaching hospital of the University of Western Ontario, invites applications for a full time position in the Division of Neurology, Department of Clinical Neurological Sciences. Victoria Hospital is an 800-bed acute care teaching hospital affiliated with the University of Western Ontario and is the regional centre for critical care, neuromuscular disease, oncology, and pain services. Applicants must be Fellows of the Royal College of Physicians and Surgeons of Canada and eligible for licensure in the province of Ontario. The successful candidate must be an excellent clinician with a demonstrated commitment to teaching and to clinical or basic research, preferably with an interest in neuro-critical care, pain, or complementary discipline. Senior residents willing to pursue fellowship training, preparatory to an academic career, are encouraged to express interest. Academic rank, salary and contractual arrangements will be commensurate with experience and qualifications. Competition will close within 90 days of this advertisement.

Submit curriculum vitae and the names of three references to:

Dr. J. Gregory Cairncross
Chief, Department of Clinical Neurological Sciences
Victoria Hospital
375 South Street
London, Ontario, Canada
N6A 4G5

In accordance with Canadian immigration requirements, this advertisement is directed to Canadian Citizens and Permanent Residents of Canada. The University of Western Ontario is committed to employment equity, welcomes diversity in the workplace, and encourages applications from all qualified individuals including women, members of visible minorities, aboriginal persons, and persons with disabilities.

NEUROSURGEON

The Division of Neurosurgery, Sunnybrook Health Science Centre, University of Toronto, is seeking an academic, geographical full-time neurosurgeon. Interest and experience in neuro-trauma or neuro-oncology and related research preferred.

Salary and academic rank will be commensurate with experience and qualification.

Candidates must have senior specialty qualification in their country of current practice, must hold or be eligible for certification in neurosurgery by the Royal College of Physicians and Surgeons of Canada, and for licensure by the College of Physicians and Surgeons of Ontario.

Applications will be accepted until the position is filled.

Interested candidates should apply, enclosing a curriculum vitae to:

Dr. D.W. Rowed
Head, Division of Neurosurgery
Sunnybrook Health Science Centre
2075 Bayview Avenue
North York, Ontario
M4N 3M5

FELLOWSHIP IN MOVEMENT DISORDERS

A Clinical Fellowship in Movement Disorders is available at The University of Calgary and Foothills Hospital starting July 1, 1994. The candidate will be expected to participate actively in clinical research and patient management. He/she must have completed a Neurology Training Program.

For further information contact:

Dr. O. Suchowersky
Director, Movement Disorders Clinic
UCMC, Area 3, 3350 Hospital Dr. N.W.
Calgary, Alberta
T2N 4N1

Ph: (403) 670-4364

Fax: (403) 283-2907

Alzheimer / ALS Neurologist

The University of Toronto seeks a neurologist for GFT position at The Toronto Hospital and the Centre for Research in Neurodegenerative Diseases. Primary responsibilities will be clinical investigation and drug trials in Alzheimer's disease and motor neuron disease. The neurologist will be in charge of developing a clinic, disease registry, and multidisciplinary team care. University rank will be commensurate with experience. In accordance with its employment equity policy, the University of Toronto encourages applications from qualified women and men, 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. Applicants should be eligible for certification in Neurology by the Royal College of Physicians and Surgeons of Canada. Interested individuals should forward CV and letters of reference to:

Dr. Donald McLachlan, Director
Centre for Research in Neurodegenerative Diseases
Tanz Neuroscience Building
University of Toronto
6 Queen's Park Cres. W.
Toronto, Ontario, Canada M5S 1A8

Miles Prize in Neurocritical Care

- Awarded annually to a resident or fellow in a Canadian training program in neurology, pediatric neurology or neurosurgery for the best paper in neurocritical care.
- Provides up to \$2,000 for travel, registration and accommodation expenses for the Canadian Congress of Neurological Sciences Meeting. (Recipients from the same city as the Congress meeting will receive an equivalent educational award).
- Research can be clinical or basic science but should relate to an aspect of neurocritical care (intensive or critical care neurology or neurosurgery).
- Supervisor should be a member of Canadian Neurocritical Care Group.
- Manuscript should follow guidelines for publication in the Canadian Journal of Neurological Sciences.
- Deadline: May 1, 1994.
- Send manuscript or write for further information to:

Dr. R. Moulton, Secretary
Canadian Neurocritical Care Group
St. Michael's Hospital
38 Shuter Street
Toronto, Ontario M5B 1A6

NEUROSURGEON The University of Manitoba

The Department of Surgery, Faculty of Medicine, University of Manitoba and the Health Sciences Centre and St. Boniface General Hospital are seeking a contingent geographic full-time Neurosurgeon.

Candidates must have Senior Specialty qualifications in neurosurgery in the country of current practice and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Eligibility for, or certification in, Neurosurgery by the Royal College of Physicians and Surgeons of Canada is required.

Specific requirements include the following:

Commitment to Academic Neurosurgery in the provision of exemplary advanced neurosurgical care, research, and residency training. Salary and academic rank will be commensurate with experience and qualifications.

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

Interested candidates should apply, enclosing a curriculum in vitae in writing to:

Dr. R.J.W. Branchard,
Professor and Head, Department of Surgery
Health Sciences Centre
GC411-820 Sherbrook Street
Winnipeg, Manitoba, Canada R3A 1R9

Closing Date: March 31, 1994 or when position is filled.

Le prix Miles en soins intensifs neurologiques

- Décerné chaque année à un résident ou à un chercheur inscrit à un programme de formation en neurologie, en neurologie pédiatrique ou en neurochirurgie pour la meilleure communication en soins intensifs neurologiques.
- Offre jusqu'à 2 000\$ en frais de déplacement, d'inscription et d'hébergement pour assister à l'assemblée du Congrès canadien des sciences neurologiques. (Les lauréats habitant la ville où a lieu le congrès recevront une bourse d'un montant équivalent.)
- La recherche doit se faire en science fondamentale ou clinique, mais elle devrait se rapporter à un aspect des soins intensifs neurologiques (soins intensifs en neurologie ou en neurochirurgie).
- Le superviseur doit faire partie du Groupe canadien pour les soins intensifs neurologiques.
- Le manuscrit doit respecter les règles en vigueur pour la publication dans le Journal canadien des sciences neurologiques.
- Date limite: Le 1^{er} mai 1994.
- Adresser les manuscrits et les demandes de renseignements à :

Dr. R. Moulton, Secretary
Canadian Neurocritical Care Group
St. Michael's Hospital
38 Shuter Street
Toronto, Ontario M5B 1A6

ADVERTISERS INDEX

Abbot

Epival – xiii, xiv

Ciba/Geigy

Tegretol – obc, ix, xvii, xviii

Deprenyl

Eldepryl – vii, xix

Dupont

Sinemet – xi, xv, xvi

Hoescht

Frisium – ibc, iii, xvi

Sandoz Canada

Organ Donation – viii

Parlodel – ifc, xii

Syntex

Ticlid – iv, v, vi

Classified Ads

– xix, xx, xxi

A well orchestrated approach



Rational therapy with Frisium is a well orchestrated approach to complete seizure control in patients of all ages, regardless of seizure type. Adverse events with Frisium are generally mild and transient.¹ Clinically significant drug interactions are uncommon, and impairment of alertness is less pronounced with Frisium than with other benzodiazepines. Help keep these patients in harmony with their surroundings.*

Add
Frisium[®] (clobazam)
To achieve seizure control.

PAAB FRI 2698/9053E

* Please consult precautions statement in Product Monograph.

 , Hoechst and ®, Reg. Trademarks of Hoechst AG, Germany

Hoechst Canada Inc., Montreal H4R 2E8

Hoechst 



There are ways of telling when a young epilepsy patient is on Tegretol® CR.

Excellent Seizure Control.

☑ Tegretol® CR (controlled-release carbamazepine) controls seizures in many patients—with little impact on cognitive function.^{1,2} Tegretol CR can leave many patients free to think clearly and do their best.^{1,2}

Consistent Blood Levels.

Tegretol CR delivers fewer “peaks and valleys” in blood levels than conventional Tegretol. That means fewer side effects and a more stable pattern of cognitive functioning.^{3,4}

Convenient B.I.D. Dosing.

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



TEGRETOL® CR.

*Helping epilepsy patients reach
their full potential.*

Geigy

Mississauga, Ontario L5N 2W5

PAAB
CCPP

MEMBER
PMAC

G-93095