Section 6 describes interictal studies of migraine with aura, while part 7 is concerned with interictal studies of migraine without aura. Techniques involved are SPECT and measurement of cerebral blood flow.

Part 8 is devoted to transcranial doppler studies in migraine starting with a chapter by Rune Aaslid the inventor of transcranial doppler technique.

Part 9 concerns cluster headaches, studies with HMPAO technetium are described as well as conventional cerebral blood flow studies and transcranial doppler ulnasonography.

Finally, there is a section concerning other types of headache as well as the effects of drugs such as Sumatriptan and Ergotamine on cerebral blood flow.

What is one to make of such a volume? It is an encyclopedic collection of almost every study of cerebral vascular mechanisms in migraine and other headaches. It contains sections of variable quality but overall the general standard of the book is excellent. The editor is to be highly commended for his ability to synthesize the different findings and for adding at the end of each section a summary trying to bring together all the frequently disperate finds. This book is essential for anybody interested in both basic and clinical research in the area of headache and it demonstrates the coming of age of migraine research.

M.J. Gawel
Toronto, Ontario

INTRACEREBRAL HEMATOMAS. First Edition. 1992. Edited by Howard H. Kaufman. Published by Raven Press. 240 pages. $144 Cdn. approx.

This book is, for the most part, a collection of reviews of topics related to cerebral hemorrhage by various experts. As expected, the individual chapters are of uneven scholarship and usefulness. Little is novel and most of the information can be obtained elsewhere either from the original articles on which the reviews are based, or in current, standard textbooks of neurology and neurosurgery where most of the topics are also addressed. The volume of the book is, therefore, to collate this material within two hard covers. There is a discussion of the incidence of stroke and the relative incidence of intracerebral hemorrhage, and of the risk factors of the latter, focusing mainly on arterial hypertension. There is a very useful review of various animal models of intracerebral hemorrhage with succinct discussions of the methodology and results from individual studies. There is a short review of the inter-relationship of the brain and blood pressure. Most useful are an extensive and expert discussion of the clinical features of intercerebral hemorrhage; and an extensive and extremely well illustrated chapter on the radiological aspects of cerebral hematomas. Infectious aneurysms are succinctly addressed, as are intracerebral hematomas associated with brain tumours. Special attention is given to pituitary lesions and pituitary apoplexy in a well illustrated chapter. The large literature on intracranial hemorrhage during pregnancy is well reviewed. Especially timely is the discussion of drug-induced intracerebral hemorrhage; and there is an interesting discussion of intracerebal hematomas in childhood. Treatment, especially of hypertensive hemorrhage, in the North-American context, is neglected, a major deficiency of the book that detracts significantly from its usefulness. There is a discussion of stereotactic aspiration of cerebral hematomas, with or without fibrinolysis, and an extensive discussion of treatment attitudes in Japan where a large experience has been gathered. Other topics are also addressed. One would wish for a more complete discussion on pathological changes and physiological aspects of hypertensive cerebrovascular disease, and a more extensive discussion of amyloid angiopathy.

This book will be useful to medical students rotating on neurology or neurosurgery and to residents preparing fellowship examinations.

Richard Leblanc
Montreal, Quebec

CLINICAL BRAIN IMAGING: PRINCIPALS AND APPLICATIONS. First Edition. 1992. Edited by John C. Mazziotta and Sid Gilman. Published by F.A. Davis Company. 480 pages. $144 Cdn. approx.

This book is intended for physicians in training and practicing clinicians, the objective is to provide an up-to-date review of "CT-based techniques". The first few chapters deal with physics, the remainder with clinical application of various imaging techniques.

Basic principles and physics of CT, MRI, PET and SPECT are covered in first four chapters. The chapter on CT contains a lot of material on high dose/delayed high dose and dynamic enhanced CT techniques which find little application in current practice. The chapter of MRI seems quite old, with disproportionate discussion of permanent and resistive magnets and little on superconductive magnets which certainly represent the state of the art. The images presented are poor quality and obviously out-dated. The preface states that these chapters are written in language "that should be understood by all physicians". The intended audience of this book will probably not find this to be the case, particularly the lengthy discussion of tracer kinetic modelling.

The remainder of the book deals with clinical applications of neuroimaging techniques. The chapters are broken down by disease categories e.g., epilepsy, neoplastic disorders etc. Throughout these chapters, there is a very heavy emphasis on functional neuroimaging, particularly PET and SPECT. The MR images tend to be of poor quality throughout these chapters, excluding the chapter on white matter disease.

While it is a very difficult task to write a book on neuroimaging which is truly up-to-date by the time it is published, this book contains material which is clearly out-dated. It fails to reflect the current central role of magnetic resonance imaging. In general, practicing clinicians will not find this to be a useful addition to their library. This volume will appeal to those who have special interest in functional neuroimaging, particularly PET and SPECT.

Robert J. Sevick
Calgary, Alberta

NEUROTOXICOLOGY. 1992. Edited by Hugh A. Tilson and Clifford L Mitchell. Published by Raven Press, New York. 400 pages. $130 Cdn. approx.

This book is not a text describing neurologic or psychiatric disorders that result from exposure to toxins under the usual headings of incidence, etiology, pathogenesis, clinical features,

diagnosis, treatment and prognosis. Rather, it is the 15th in a series entitled "Target Organ Toxicology", the purpose of which is "to review the morphology, physiology, biochemistry, cellular biology, and developmental aspects of (toxic exposure in) various target organs". It is intended to include "a description of the tests routinely used to determine toxicity, evaluation of the feasibility of assays used in the assessment of hazards, and the need for applying recent advances in the basic sciences to the development and validation of new testing procedures." It is also to include a description of the incidence of chemically-induced human disease, the reliability of laboratory data extrapolation to humans, and the methods currently used to estimate human risks". As the orientation and breadth of the subject matter covered suggests, the editors are: a director of a neurotoxicology division in a laboratory of the US Environment Protection Agency, and member of a molecular and integrative neuroscience division of the National Institute of Environmental Health Science. Authors of individual chapters are largely scientists from laboratories concerned ultimately with assessment of risks and the regulatory responsibilities of government, particularly with regard to industrial products.

Included also are authors from departments of pharmacology, psychology, neurology and neuropathology with a collaborative expertise in neurotoxicology. Chapters give comprehensive discussions of methods of assessing toxicity ranging from molecular and biochemical, through cell culture, morphologic, neurophysiologic and neuropsychologic techniques to more general discussions. A chapter of special importance and with particular relevance to clinical neurology is devoted to toxicity in the developing brain. Neurotoxicology, always a vital interest to clinical neurology, has never emerged as a clinical subspecialty. The obvious reason for this is the pervasive role of toxins in disease of the nervous system and the wide interdisciplinary collaboration required for study and management of these disorders. Neuroscientists, clinicians and non-clinicians alike, are unavoidably amateur neurotoxicologists. With the increasing recognition of new toxic syndromes (e.g., domoic acid, MPTP, aluminum, hydantoin, isotretinoin) neuroscientists will increasingly be drawn into the socially and politically-charged subject matter that is central to the discipline of neurotoxicology. This discipline is concerned with adverse endpoints and it is interesting to learn that these are defined by the National Academy of Sciences as "impairment of functional capacity or a decrement of the ability to compensate for additional stress, a detectable decrement of the ability to maintain homeostasis, or enhancement of susceptibility to the deleterious effects of environmental influences". Implications for compensation are obvious. The orientation of this book has brought together a great deal of the interesting and eclectic material of neurotoxicology. Although of primary interest to toxicologists, there is much here of interest to neuroscientists of all stripes. It is nicely packaged in the current Raven Press format.

John R. Wherrett
Toronto, Ontario

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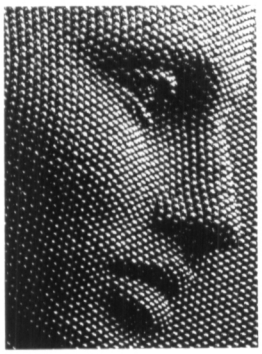

SIBELIUM flunarizine hydrochloride
THERAPEUTIC CLASSIFICATION Selective Calcium-Entry Blocker

ACTION AND CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

Table 1: Pharmacokinetic parameters of flunarizine in healthy volunteers

	No. of Doses	Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC (ng/mL*h)	t½α (h)	Clp (mL/min)	t½β (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[e]	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 migraine with and without aura. 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.

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.

Excessive sedation can occur when alcohol, hypnotics or tranquilizers are taken simultaneously with SIBELIUM.

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 frequenlty, 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 WARNINGS).

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 WARNINGS).

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

On the basis of the pharmacological properties of the drug, sedation and asthenia may be expected to occur. A few cases of acute overdosage (up to 600 mg in one intake) have been reported and the observed symptoms included central nervous system effects (e.g. sedation, confusion and agitation) and cardiovascular effects (e.g. tachycardia). Treatment of acute overdosage consists of charcoal administration, induction of emesis or gastric lavage, and supportive measures. No specific antidote is known.

DOSAGE AND ADMINISTRATION

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

Duration of Therapy

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

DOSAGE FORMS

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

Product monograph available on request.

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See pages viii, ix

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Epival*

divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Musculoskeletal: Weakness has been reported.

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

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

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

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

Other: Edema of the extremities has been reported.

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

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

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

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

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

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

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

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

Product monograph available on request.

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ABBOTT LABORATORIES, LIMITED
P.O. BOX 6150 STATION A
MONTRÉAL, QUÉBEC H3C 3K6

See page xvi

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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

P SERC®

(Betahistine hydrochloride) TABLETS

INDICATIONS: SERC may be of value in reducing the episodes of vertigo in Meniere's disease. No claim is made for the effectiveness of SERC in the symptomatic treatment of any form of vertigo other than that associated with Meniere's disease. It also has not been established that betahistine has any effect on other manifestations of Meniere's disease.

CONTRAINDICATIONS: Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using SERC. Although no causal relation has been established, SERC is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. SERC is also contraindicated in patients with pheochromocytoma.

PRECAUTIONS: Although clinical intolerance to SERC by patients with bronchial asthma has not been demonstrated, caution should be exercised if the drug is used in these patients.

SERC should not be used concurrently with antihistamine agents, since no information is available with regard to the possible interaction of these drugs.

USE IN PREGNANCY: The safety of SERC in pregnancy has not been established. Therefore, its use in pregnancy or lactation, or in women of child-bearing age requires that its potential benefits be weighed against the possible risks.

ADVERSE REACTIONS: Occasional patients have experienced gastric upset, nausea and headache.

DOSAGE AND ADMINISTRATION: The usual adult dosage has been one to two tablets (4 mg each) administered orally three times a day. The dosage has ranged from two tablets per day to eight tablets per day. No more than eight tablets are recommended to be taken in any one day.

SERC (betahistine hydrochloride) is not recommended for use in children. As with all drugs, SERC should be kept out of reach of children.

HOW SUPPLIED: Scored tablets of 4 mg each in bottles of 100 tablets.

Full Product Monograph available upon request.

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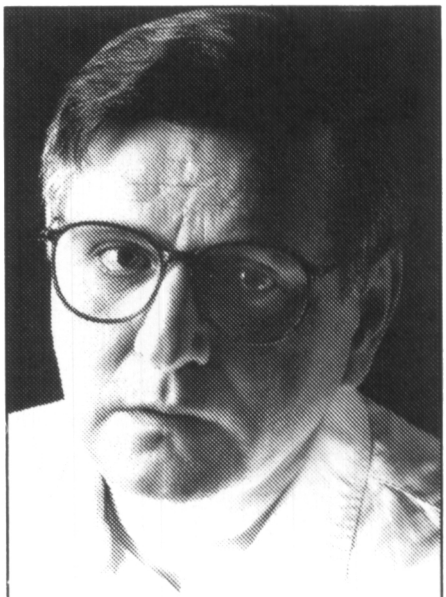

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SINEMET® CR

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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 intraocularpressure 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 tricylic antidepressants and carbidopa-levodopa preparations. (For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.)

Other drugs: Although specific interaction studies were not performed with other concomitant drugs, in clinical trials of SINEMET® CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, *thiazides, digoxin, H_2 antagonists, salicylates and other nonsteroidal anti-*inflammatory drugs. SINEMET® CR was also used with other antiparkinson agents (see DOSAGE and ADMINISTRATION).

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

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

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

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

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

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

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

Abnormalities in various laboratory tests have occurred with SINEMET® *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.

In the event of overdosage, general supportive measures should be employed, along with immediate gastric lavage if ingestion was recent. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient observed carefully for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possiblity 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 (levodopa 200 mg/carbidopa 50 mg per tablet). The daily dosage of SINEMET® CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

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

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

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

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

Guideline for Initial Conversion from SINEMET® to SINEMET® CR

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

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

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

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

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

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

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

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

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

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

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CANADIAN SOCIETY OF CLINICAL NEUROPHYSIOLOGISTS

EXAMINATION IN ELECTROENCEPHALOGRAPHY

The Examining Committee is pleased to announce the names of successful candidates in the second CSCN EEG Examination held in June 1992:

Dr. Richard Desbiens
Dr. Shang-Yeong Kwan
Dr. Wei Ling Lee
Dr. Angus Wilfong

SCHEDULE FOR 1993 EXAMINATIONS

Multiple-choice written in home city:
Saturday, May 1, 1993

Oral examination for successful written candidates:
June 1993 in association with Canadian Congress of Neurological Sciences at Toronto

Write to: Dr. Warren T. Blume
CSCN, Examining Committee
University Hospital, EEG Dept.
339 Windermere Road
London, Ontario N6A 5A5

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The Saskatchewan Stroke Research Centre at the University of Saskatchewan, with eight active faculty members, offers a one or two year fellowship in cerebrovascular research.

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For further information, address inquiries to:

Ashfaq Shuaib, M.D., F.R.C.P.C.
Saskatchewan Stroke Research Centre
Royal University Hospital
Saskatoon, Saskatchewan
Canada S7N 0X0

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