

#### **Controlled-Release Tablets** Antiparkinson Agent

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

levodona/decarboxylase inhibitors or levodona alone is limited SINEMET<sup>60</sup> 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<sup>GD</sup> CR.

SINEMET<sup>GO</sup> CR should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hema-tologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or

As with levodopa, SINEMET<sup>69</sup> CR should not be given when administration of a sympathomimetic amine is contraindicated. SINEMET<sup>GO</sup> CR is contraindicated in patients with known hyper-

sensitivity to any component of this medication.

Because levodopa may activate a malignant melanoma, SINEMET<sup>®</sup> 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 SINEMETTO (levodopa and carbidopa), this medication must be discontinued at least 8 hours before therapy with SINEMETO CR is started. (For appropriate dosage substitutions, see DOSAGE AND ADMINISTRATION).

As with levodopa or SINEMET<sup>(4)</sup>, SINEMET<sup>(4)</sup> 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mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly.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 neuroloptics. Care should be exercised in administering SINEMET<sup>®</sup> 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<sup>®</sup> 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<sup>GO</sup> 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 in Product Monograph). Therefore, use of SINEMET<sup>®</sup> 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<sup>®</sup> 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 $^{\odot}$  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

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papaverine. Patients taking these drugs with SINEMET  $\textcircled{\mbox{\sc b}}$  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, propranolo), thiazides, digoxin, H<sub>2</sub> antagonists, salicylates and other nonsteroidal antiinflammatory drugs. SINEMET<sup>(s)</sup> 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<sup>GO</sup> 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: Bilter 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 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.

Dosage and Administration: SINEMET(e) CR (levodopa and carbidopa) Tablets contain a 4:1 ratio of levodopa to carbidopa. SINEMET $^{co}$  CR 200/50 contains levodopa 200 mg/carbidopa 50 mg per tablet. SINEMET<sup>©</sup> CR 100/25 contains levodopa 100 mg/carbidopa 25 mg per tablet. The daily dosage of SINEMET<sup>©</sup> 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<sup>GD</sup> CR 200/50 may be administered as whole or as half tablets. SINEMET<sup>®</sup> 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<sup>®</sup> CR is being administered, although their dosage may have to be adjusted. The delayed onset of action with SINEMET<sup>®</sup> CR may require the supplemental use of conventional SINEMET<sup>®</sup> 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 SINEMETVO CR 200/50 is shown in the following table: . . .. . .

Gu:deline for Initial Convei	rsian
from SINEMET® to SINEMET®	CR 200/50

SINEMET© Total Daily Dose* Levodopa (mg)	SINEMET® CR 200;50 (levadopa 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 Dasage for Patients Currently Treated with Levadopa Alone. Levadopa must be discontinued at least eight hours before therapy with SINEMET<sup>IN</sup> CR 200/50 is started. SINEMET<sup>IN</sup> CR should be substituted at a dosage that will provide approximately 25% of the previous levadopa 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 SINEMETC' 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 litration when necessary in patients receiving SINEMETCO CR 2C0/50. The initial recommended dose is 1 tablet of SINEMET<sup>120</sup> CR 100/25 twice daily, for patients who require more levelopa, a daily dose of 1 to 4 tablets of SINEMET<sup>2</sup> 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.

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 of SiNEMET CR 200/50 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 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.

Availability of Dosage Form: 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

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## PRESCRIBING INFORMATION

NAME OF DRUG: EPIVAL<sup>o</sup> (divalproex sodium) Enteric-Coated Tablets

THERAPEUTIC CLASSIFICATION: Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY: EPIVAL<sup>©</sup> (divalproex sodium) has anticonvulsant properties, and is chemically related to valproic acid. Although its mechanism of action has not yet been established, it has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown. EPIVAL<sup>©</sup> dissociates into valproic acid in the gastrointestinal tract.

Peak serum levels of valproic acid occur in 3 to 4 hours.

The serum half-life ( $t_{M}$ ) of valproic acid is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other drugs capable of enzyme induction. Enzyme induction may result in enhanced clearance of valproic acid by olucuronidation and microsomal oxidation. Because of these changes in valproic acid clearance, monitoring of valproate and concomitant drug concentrations should be intensified whenever enzyme-inducing drugs are introduced or withdrawn. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. Increases in doses may result in decreases in the extent of protein binding and variable changes in valproic acid clearance and elimination. In epilepsy, the therapeutic plasma concentration range is believed to be from 50 to 100 µg/mL. Occasional patients may be controlled with serum levels lower or higher than this range. A good correlation has not been established between daily dose, serum level and therapeutic effect. In placebo-controlled clinical studies in acute mania, 79% of patients were dosed to a plasma concentration between 50 µg/mL and 125 µg/mL. Protein binding of valproate is saturable ranging from 90% at 50 µg/mL to 82% at 125 µg/mL.

Elimination of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the faces and expired air. Very little unmetabolized parent drug is excreted in the urine. The principal metabolite formed in the liver is the glucuronide conjugate. Other metabolites in the urine are products of C-3, C-4 and C-5 oxidation. The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxy-pentanoic acid, 2-propyl-3-hydroxy-pentanoic acid and 2-propyl-4-hydroxy-pentanoic acid.

(See WARNINGS regarding statement on fatal hepatic dysfunction.)

#### INDICATIONS AND CLINICAL USE:

Epilepsy: EPIVAL<sup>o</sup> (divalproex sodium) is indicated for use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal and is useful in primary generalized seizures with tonic-clonic manifestations. Divalproex sodium may also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

Acute Mania: EPIVAL<sup>o</sup> (divalproex sodium) is indicated in the treatment of the manic episodes associated with bipolar disorder (DSM-III-R).

The effectiveness of EPIVAL<sup>o</sup> in long-term use, that is for more than 3 weeks, has not been systematically evaluated in controlled trials. EPIVAL<sup>o</sup> is not indicated for use as a mood stabilizer in patients under 18 years of age.

CONTRAINDICATIONS: EPIVAL<sup>o</sup> (divalproex sodium) should not be administered to patients with hepatic disease or significant dysfunction; it is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. These incidences usually occurred during the first six months of treatment with valproic acid. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease.

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<sup>©</sup> is to be used for the control of seizures in children two years old or younger, it should be used with *extreme caution* and as a sole agent. The benefits of therapy should be weighed against the risks.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, vomiting, and in epileptic patients, loss of seizure control. 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<sup>o</sup> (divalproce 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 when administering EPIVAL® to 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 decreases in concentration and serum ammonia for increases in concentration. If changes occur, divalproex sodium should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. The benefit of improved symptom control at higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Use in pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of human females 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 acidexposed 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 (ANEN-CEPHALY AND SPINA BIFIDA).

Animal studies have demonstrated valproic acid-induced teratogenicity (see *Reproduction and Teratology* under TOXICOLOGY), 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 antiepileptic drugs and an elevated 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 and/or palate, cranifacial abnormalities and neural tube defects. Nevertheless, the great majority of mothers receiving antiepileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed antiepileptics. Some reports indicate a possible similar association with the use of other antiepileptic 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 hicher incidence of birth defects.

Patients taking valproic acid may develop clotting abnormalities. If valproic acid is used in pregnancy, the clotting parameters should be monitored carefully.

Antiepileptic 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 childbearing 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 antiepileptic medication is in doubt, appropriate consultation is indicated.

Risk-benefit must be carefully considered when treating women of childbearing age for bipolar disorder.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

Use in 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<sup>®</sup> (divalproex sodium). It is not known what effect this may have on a nursing infant.

Fertility: The effect of valproate on testicular development and on sperm production and fertility in humans is unknown. (See TOXI-COLOGY: Fertility, for results in animal studies.)

Long-term animal toxicity studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for man is unknown at present.

#### PRECAUTIONS:

Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia, inhibition of the second phase of platelet aggregation, platelet counts and coagulation tests are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving EPIVAL<sup>o</sup> (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemosta-

Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of EPIVAL<sup>®</sup> (divalproex sodium) 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 divatproex sodium should be discontinued.

EPIVAL<sup>®</sup> (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.

Renal Impairment: Renal impairment is associated with an increase in the unbound fraction of valproate. In several studies, the unbound fraction of valproate in plasma from renally impaired patients was approximately double that for subjects with normal renal function. Hemodialysis in renally impaired patients may remove up to 20% of the circulatino valproate.

Use in the Elderly: The safety and efficacy of EPIVAL<sup>o</sup> in elderly patients with epilepsy and mania has not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with EPIVAL<sup>o</sup> in this population.

Driving and Hazardous Occupations: EPIVAL<sup>o</sup> (divalproex sodium) 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.

 $\mbox{Drug}$  Interactions: EPIVAL\* (divalproex sodium) may potentiate the CNS depressant action of alcohol.

The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine and dicumarol) may result in alteration of serum drug levels.

Aspirin and Warfarin: Caution is recommended when EPIVAL® is administered with drugs affecting coagulation (e.g., aspirin and warfarin). (See ADVERSE REACTIONS.)

Phenobarbital: 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, it possible, and the barbiturate dosage decreased, if indicated.

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

Phenytoin: There is conflicting evidence regarding the interaction of valproic acid with phenytoin. 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. There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Because EPIVAL<sup>o</sup> (divalproex sodium) may interact with concurrently administered drugs which are capable of enzyme induction, periodic serum level determinations of these drugs are recommended during the early part of therapy.

Clonazepam: The concomitant use of valproic acid and clonazepam may produce absence status in patients with a history of absencetype seizures.

Oral contraceptives: Evidence suggests that there is an association between the use of certain drugs capable of enzyme induction and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing antiepileptic drugs effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. Valproic acid is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of valproic acid with oral contraceptives are minimal.

Seizures: In addition to enhancing central nervous system (CNS) depression when used concurrently with valproic acid, tricyclic antidepressants, MAO Inhibitors, and antipsychotics may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

Carbamazepine: Concomitant use of carbamazepine with valproic acid may result in decreased serum concentrations and hall-life of valproate due to increased metabolism induced by hepatic microsomal enzyme activity. Valproate causes an increase in the active 10, 11 -epoxide metabolite of carbamazepine by inhibition of its breakdown. Monitoring of serum concentrations is recommended when either medication is added to or withdrawn from an existing regimen. Changes in the serum concentration of the 10, 11 -epoxide metabolite of carbamazepine, however, will not be detected by routine serum carbamazepine assay.

Cimetidine: Cimetidine may decrease the clearance and increase the half-life of valproic acid by altering its metabolism. In patients receiving valproic acid, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The valproic acid dose should be adjusted accordingly.

Chlorpromazine: A single study has shown that the concomitant use of chlorpromazine with valproic acid may result in a decrease in valproic acid clearance. Valproic acid serum concentrations and effects should be monitored when valproic acid is co-administered with chlorpromazine due to possible inhibition of valproic acid metabolism.

Selective serotonin re-uptake inhibitors (SSRIs): Some evidence suggests that SSRIs inhibit the metabolism of valproate, resulting in higher than expected levels of valproate.

Tricyclic antidepressants: The metabolism of amitriptyline and nortriptyline after a single dose of amitriptyline (50 mg) was inhibited by multiple dosing with valproic acid (500 mg twice daily) in sixteen healthy male and female volunteers. For the sum of amitriptyline and nortriptyline plasma concentrations, in the presence of valproic acid, the mean C<sub>max</sub> and AUC were increased by 19% and 42%, respectively.

Lithium: In a double-blind, placebo-controlled, multiple dose crossover study in 16 healthy male volunteers, pharmacokinetic parameters of lithium were not altered by the presence or absence of EPIVAL<sup>o</sup>. The presence of lithium, however, resulted in an 11%-12% increase in the AUC and  $C_{max}$  of valproate.  $T_{max}$  was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance.

Benzodiazepines: Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations. In two small studies in healthy volunteers, valproate produced a 17% decrease in the clearance of lorazepam, and 26% decrease in the clearance of unbound diazepam. Displacement of diazepam from plasma protein binding sites may also occur. During valproate administration the unbound fraction of diazepam in the serum increased approximately twofold.

#### ADVERSE REACTIONS:

Epilepsy: The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other antiepileptics, 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 antiepileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor (may be dose-related), 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, photosensitivity, generalized pruritus, erythema multiforme, Stevens-Johnson syndrome and petechiae have rarely been noted.

Endocrine: There have been reports of irregular menses and secondary amenorrhea, breast enlargement, galactorrhea and parotid gland swelling in patients receiving valproica acid. Abnormal thyroid function tests have been reported (see PRECAUTIONS).

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported. Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (see PRECAU-TIONS). This may be reflected in altered bleeding time. Petechiae, bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis, macrocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia, including macrocytic with or without folate defliciency, bone marrow suppression and acute intermittent porphyria have been reported.

Hepatic: Minor elevations of transaminases (e.g., SGOT and SGPT) and LOH 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), hyponatremia and inappropriate ADH secretion. Hyperglycinemia has been reported and associated with a fatal outcome in a patient with preexisting non-ketolic hyperglycinemia.

Genitourinary: Enuresis

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

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established.

Other: Edema of the extremities has been reported.

Bipolar Disorder: The incidence of adverse events has been ascertained based on data from two short-term (21 day) placebo-controlled clinical trials of divalproex sodium in the treatment of acute mania, and from two long-term (up to 3 years) retrospective open trials.

Most Commonly Observed: During the short-term placebo-controlled trials, the six most commonly reported adverse events in patients (N=89) exposed to divalproex sodium were nausea (22%), headache (21%), somnoience (19%), pain (15%), vorniting (12%), and dizziness (12%).

In the long-term retrospective trials (634 patients exposed to divalproex sodium), the six most commonly reported adverse events were somnolence (31%), tremor (29%), headache (24%), asthenia (23%), diarrhea (22%), and nausea (20%).

Associated with Discontinuation of Treatment: In the placebo-controlled trials, adverse events which resulted in valproate discontinuation in at least one percent of patients were nausea (4%), abdominal pain (3%), somnolence (2%), and rash (2%).

In the long-term retrospective trials, adverse events which resulted in valproate discontinuation in at least one percent of patients were alopecia (2.4%), sommolence (1.9%), nausea (1.7%), and termor (1.4%). The time to onset of these events was generally within the first two months of initial exposure to valproate. A notable ecception was alopecia, which was first experienced after 3-6 months of exposure by 8 of the 15 patients who discontinued valproate in response to the event.

Controlled Trials: Table 1 summarizes those treatment-emergent adverse events reported for patients in the placebo-controlled trials when the incidence rate in the divalproex sodium group was at least 5%. (Maximum treatment duration was 21 days; maximum dose in 8% of patients was between 1000 mg - 2500 mg per day).

## Table 1

Treatment-Emergent Adverse Event Incidence ( $\geq$  5%) in Short-Term Placebo-Controlled Trials

Body System/Event	Percentage of Patients		
	divalproex sodium (N=89)	placebo (N=97)	
Body as a Whole		_	
Headache	21.3	30.9	
Pain	14.6	15.5	
Accidental injury	11.2	5.2	
Asthenia	10.1	7.2	
Abdominal Pain	9.0	8.2	
Back Pain	5.6	6.2	
Digestive System			
Nausea	22.5	15.5	
Vomiting	12.4*	3.1	
Diarrhea	10.1	13.4	
Dyspepsia	9.0	8.2	
Constipation	7.9	8.2	
Nervous System			
Somnolence	19.1	12.4	
Dizziness	12.4	4.1	
Tremor	5.6	6.2	
Respiratory System			
Pharyngitis	6.7	9.3	
Skin and Appendages			
Rash	5.6	3.1	

\*Statistically significant at p≤0.05 level.

Adverse Events in Elderly Patients: In elderly patients (above 65 years of age), there were more frequent reports of accidental injury, infection, pain, and to a lesser degree, somnolence and tremor, when compared to patients 18-65 years of age. Somnolence and tremor tended to be associated with the discontinuation of valproate.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: In a reported case of overdosage with valproic acid after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse stowing, compatible with the state of consciousness. The patient made an uneventful recovery. Naloxone has been reported to reverse the CNS depressant effects of valproic acid overdosage.

Because naloxone could theoretically also reverse the antiepileptic effects of EPIVAL®, it should be used with caution in patients with epilepsy.

Since EPIVAL® tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

#### DOSAGE AND ADMINISTRATION:

Epilepsy: EPIVAL<sup>©</sup> (divalproex sodium) is administered orally. 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 is 125 mg or greater, it should be given in a divided regimen (see Table 2).

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

> Table 2 Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily	Dosage (mg)		g) pie seid
kg	lb	Dose (mg)	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	1000	250	250	500
75-89.9	165-197.9	1250	500	250	500

As the dosage of divalproex sodium is raised, blood levels of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS, under Drug Interactions).

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.

Acute Mania: The recommended initial dose is 250 mg three times a day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations.

In placebo-controlled trials, 84% of patients received and tolerated maximum daily doses of between 1000 mg/day to 2500 mg/day. The maximum recommended dosage is 60 mg/kg/day.

The relationship of plasma concentration to clinical response has not been established for EPIVAL<sup>o</sup>. In controlled clinical studies, 79% of patients achieved and tolerated serum valproate concentrations between 50 µg/mL and 125 µg/mL.

When changing therapy involving drugs known to induce hepatic microsomal enzymes (e.g., carbamazepine) or other drugs with valproate interactions (see PRECAUTIONS, Drug Interactions), it is advisable to monitor serum valproate concentrations.

Conversion from Depakene® to EPIVAL®: EPIVAL® (divalproex sodium) dissociates into valproic acid in the gastrointestinal tract. Divalproex sodium tablets are uniformly and reliably absorbed, however, because of the enteric-coating, absorption is delayed by an hour when compared with Depakene (valproic acid) capsules. The bioavailability of divalproex sodium tablets is equivalent to that of Depakene (valproic acid) capsules.

In patients previously receiving Depakene<sup>o</sup> (valproic acid) therapy, EPIVAL<sup>o</sup> should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on EPIVAL<sup>o</sup>, a dosing schedule of two or three times a day may be elected in selected patients. PHARMACEUTICAL INFORMATION:

#### Dava Cubatanaa

Drug Substance	
Tradename:	EPIVAL°
Proper Name:	Divalproex sodium
USAN Names:	INN: Valproate semisodium BAN: Semisodium valproate
Chemical Name:	Sodium hydrogen bis (2-propylpentanoate) or Sodium hydrogen bis (2-propylvalerate)
Molecular Weight:	310.14 Molecular Formula: C <sub>16</sub> H <sub>31</sub> NaO <sub>4</sub>
Structural Formula	а:
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> —	Сн—Сн₂Сн₂Сн₃ 

но<sup>∕с́</sup>≈о °<sub>€с</sub>∕<sup>0- №а+</sup>

CH3CH2CH2-CH-CH2CH2CH3

Description: Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. It is a white powder with a characteristic odor, freely soluble in many organic solvents and in aqueous alkali solutions.

Non-Medicinal Ingredients: EPIVAL® Enteric-Coated Tablets: Cellulosic polymers, silica gel, diacetylated monoglycerides, povidone, pregetatinized starch (contains corn starch), talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:

125 mg tablets: FD&C Blue No.1 and FD&C Red No. 40

250 mg tablets: FD&C Yellow No. 6 and iron oxide

500 mg tablets: D&C Red No. 30, FD&C Blue No. 2, and iron oxide. Storage Recommendations: Store between 15°- 30°C (59°- 86°F).

AVAILABILITY OF DOSAGE FORMS: EPIVAL<sup>o</sup> (divalproex sodium) particle coated tablets are available as salmon-pink coloured tablets of 125 mg in bottles of 100 tablets; peach-coloured tablets of 250 mg and lavender-coloured tablets of 500 mg in bottles of 100 and 500 tablets.

INFORMATION FOR THE CONSUMER: Since EPIVAL<sup>o</sup> (divalproex sodium) may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

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ABBOTT LABORATORIES, LIMITED P.O. BOX 6150, STATION CENTRE-VILLE MONTREAL, QUÉBEC, H3C 3KB

MONTRÉAL, QUÉBEC HISCISKE
 Product Monograph available on request.
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(Carbamazepine tablets)

#### THERAPEUTIC CLASSIFICATION

1. Anticonvulsant

2. For Symptomatic Relief of Trigeminal Neuralgia 3. Antimanic

#### INDICATIONS AND CLINICAL USE

A. Epilepsy: TEGRETOL (carbamazepine) is indicated for use as an anticonvulsant drug either alone or in combination with other anticonvulsant drugs.

Carbamazepine is not effective in controlling absence, myoclonic or atonic seizures, and does not prevent the generalization of epileptic discharge. Moreover, exacerbation of seizures may occasionally occur in patients with atvoical absences.

B. Trigeminal Neuralgia: TEGRETOL is indicated for the symptomatic relief of pain of trigeminal neuralgia 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, other accepted measures must be considered. Carbamazepine is not a simple analgesic and should not be

used to relieve trivial facial pains or headaches.

C. Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders: TEGRETOL may be used as monotherapy or as an adjunct to lithium in the treatment of acute mania or prophylaxis of bipolar (manic-depressive) disorders in patients resistant to or intolerant of conventional antimanic drugs. Carbamazepine may be a useful alternative to neuroleptics in such patients. Patients with severe mania, dysphoric mania or rapid cycling who are non-responsive to lithium may show a positive response when treated with carbamazepine.

Recommendations are based on extensive clinical experience and some clinical trials versus active comparison agents.

#### CONTRAINDICATIONS

TEGRETOL (carbamazepine) should not be administered to patients with hepatic disease, a history of 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. The dosage of TEGRETOL should be low initially, and increased very gradually.

TEGRETOL should not be administered to patients presenting atrioventricular heart block.

TEGRETOL should not be administered to patients with known hypersensitivity to carbamazepine or any tricyclic compound, 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. IN THE MAJORITY OF CASES LEUCOPENIA AND THROMBOCYTOPENIA WERE TRANSIENT AND DID NOT SIGNAL THE ONSET OF EITHER APLASTIC ANEMIA OR AGRANULOCYTOSIS. 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 SIGN'S AND SYMPTOMS SUGGEST A SEVERE SKIN REACTION SUCH AS STEVEN-JOHNSON SYNDROME OR LYELL SYNDROME, WITHDRAW TEGRETOL AT ONCE. LONG-TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK. THEREFORE WEIGH THE POSSIBLE RISK 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 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 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 if required to prevent major seizures because of the risks posed, to 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, which 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, administration to the mother 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.

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, 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 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. Treatment 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 the elderly and patients with a history of liver disease. Withdraw TEGRETOL 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 xviii

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 Drug 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, 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 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. Follow such patients closely.

Occurrence of Behavioral 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. Exercise caution in alcoholics.

Use in Patients with Cardiovascular Disorders: Use TEGRETOL 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, 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 diminish or abolish the activity of certain drugs that are also metabolized in the liver. 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, 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), the dosage of TEGRETOL should be adjusted accordingly and the blood levels monitored.

Plasma levels of carbamazepine may be reduced by phenobarbitone, phenytoin, primidone, progabide, or theophylline, and possibly by clonazepam. 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 10,11epoxide; carbamazepine plasma levels should be monitored.

Carbamazepine, like other psycho-active drugs, may reduce alcohol tolerance; it is advisable to abstain from alcohol during treatment.

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

The reactions most frequently reported with TEGRETOL (carbamazepine) are CNS (e.g. drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. These 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, megaloblastic anemia, acute intermittent porphyria. reticulocytosis, folic acid deficiency, thrombocytopenic purpura, and possibly hemolytic anemia. In a few instances, deaths have occurred.

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

Dermatologic: Occasional to frequent - skin sensitivity reactions and rashes, erythematous rashes, urticaria; rare - exfoliative dermatitis and erythroderma, Steven-Johnson syndrome, systemic lupus erythematosus-like syndrome; isolated cases - toxic epidermal necrolysis (Lyell's syndrome), photosensitivity, erythema multiform and nodosum, skin pigmentation changes, pruritus, purpura, acne, diaphoresis, alopecia and neurodermatitis. Isolated cases of hirsuitism have been reported, however the causal relationship is not clear.

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, paraesthesia, muscle weakness. 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: Rare - disturbances of cardiac conduction; isolated cases - 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 sexual disturbances/impotence.

Gastrointestinal: Occasional or frequent - nausea, vomiting; occasional - dryness of the mouth and throat; rare diarrhea or constipation; isolated cases - abdominal pain, glossitis, stomatitis, anorexia.

Sense organs: Isolated cases - lens opacities, conjunctivi-

tis, 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, T, T, 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 trialvcerides.

Musculoskeletal system: Isolated cases - arthralgia, muscle pain or cramp.

Respiratory: Isolated cases - pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneu monia.

Hypersensitivity reactions: A rare delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepatosplenomegaly 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. Discontinue treatment should such hypersensitivity reactions occur.

#### DOSAGE AND ADMINISTRATION

Use in Epilepsy (See INDICATIONS): TEGRETOL may be used alone or with other anticonvulsants. A low initial daily dosage of TEGRETOL with a gradual increase in dosage adjusted to the needs of the individual patient, is advised. 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. Controlled release tablets should be prescribed as a twice-daily dosage. If necessary, three divided doses may be prescribed. Some patients have been reported to require a dosage increase when switching from tablets to CR tablets. Dosage adjustments should be individualized based on clinical response and, if necessary, plasma carbamazepine levels.

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

#### AV

AVAILABILITY OF DOSAGE FORM					
	TEGRETOL tablets 200 mg	TEGRETOL CHEWTABS 100 mg	TEGRETOL CHEWTABS 200mg	TEGRETOL CR 200 mg	TEGRETOL CR 400 mg
Colour	White	White with red specks	White with red specks	Beige-orange	Brownish- orange
Shape	Round, flat-faced and bevel-edged	Round, flat-faced and bevel-edged	Oval, biconvex	Oval, slightly biconvex	Oval, slightly biconvex
Imprint	Engraved GEIGY on one side and quadrasected on the other	Engraved GEIGY on one side and M/R with bisect on the other	Engraved GEIGY on one side and P/U with bisect on the other	C/G engraved on one side and H/C engraved on the other. Fully bisected on both sides	CG/CG engraved on one side and ENE/ENE engraved on the other. Fully bisected on both sides
Carbamazepine	200 mg	100 mg	200 mg	200 mg	400mg
Availability	Bottles of 100 & 500	Bottles of 100	Bottles of 100	Bottles of 100	Bottles of 100

Tegretol is a schedule F drug and can only be obtained by prescription from a licensed practitioner. Product Monograph available on request. September 23, 1994 REFERENCES

- 1. 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.
- Reynolds EH: Polytherapy, monotherapy, and carbam-azepine. Epilepsia 1987; 28(Suppl 3): 577-580.
- 3. Aldenkamp et al: Controlled release carbamazepine: cognitive side effects in patients with epilepsy. Epilepsia 1987; 28(Suppl 3): 507-514.

4. TEGRETOL<sup>C</sup>CR Product Monograph, August, 1992.

See pages obc, xii.

# Geigy

Geigy Pharmaceuticals Division of Ciba-Geigy Canada Ltd. Mississauga, Ontario L5N 2W5 or Dorval, Quebec H9S 1B1

CCPP

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, increased gradually by 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. Combination Therapy: When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except for phenytoin, which may be increased (See Precautions, Drug Interactions and Warnings, Pregnancy and nursing).

Use in Trigeminal Neuralgia: Initial daily dosage of 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 of 200-800 mg daily; 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. Use in Mania and Bipolar (Manic-Depressive) Disorders: The initial daily dosage should be low, 200 to 400 mg/day, administered in divided doses, although higher starting doses of 400 to 600 mg/day may be used in acute mania. This dose may be gradually increased until patient symptomatology is controlled or a total daily dose of 1600 mg is achieved. Increments in dosage should be adjusted to provide optimal patient tolerability. The usual dose range is 400 to 1200 mg/day administered in divided doses. Doses used to achieve optimal acute responses and tolerability should be continued during maintenance treat-When given in combination with lithium and ment. neuroleptics, the initial dosage should be low, 100 mg to 200 mg daily, and then increased gradually. A dose higher than 800 mg/day is rarely required when given in combination with neuroleptics and lithium, or with other psychotropic drugs such as benzodiazepines. Plasma levels are probably not helpful for guiding therapy in bipolar disorders. Stability and Storage Recommendations

Protect from heat and humidity. Keep out of reach of children.

PARKE-DAVIS



100 mg, 300 mg, 400 mg Capsules Antiepileptic Agent

#### ACTION AND CLINICAL PHARMACOLOGY

Gabapentin exhibits antiseizure activity in mice and rats both in the maximal electroshock and in the pentylenetetrazol seizure models.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but does not interact with GABA receptors, it is not metabolized to GABA or to GABA agonists, and it is not an inhibitor of GABA uptake or degradation. Gabapentin at concentrations up to 100  $\mu$ M did not demonstrate affinity for other receptor sites such as benzodiazepine, glutamate, glycine or N-methyl-D-aspartate receptors nor does it interact with neuronal sodium channels or L-type calcium channels.

The mechanism of action of gabapentin has not yet been established, however, it is unlike that of the commonly used anticonvulsant drugs.

In vitro studies with radiolabelled gabapentin have revealed a gabapentin binding site in rat brain tissues including neocortex and hippocampus. The identity and function of this binding site remain to be elucidated.

#### **Pharmacokinetics**

#### Adults:

Following oral administration of Neurontin (gabapentin), peak plasma concentrations are observed within 2 to 3 hours. Absolute bioavailability of a 300 mg dose of Neurontin capsules is approximately 59%. At doses of 300 and 400 mg, gabapentin bioavailability is unchanged following multiple dose administration. Gabapentin elimination from plasma is best described by linear pharmacokinetics. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours in subjects with normal renal function.

Plasma gabapentin concentrations are dose-proportional at doses of 300 to 400 mg q8h, ranging between 1 µg/mL and 10 µg/mL, but are less than dose-proportional above the clinical range (>600 mg q8h). There is no correlation between plasma levels and efficacy. Gabapentin pharmacokinetics are not affected by repeated administration, and steady state plasma concentrations are predictable from single dose data.

Gabapentin is not appreciably metabolized in humans, is eliminated solely by renal excretion, and can be removed from plasma by hemodialysis.

Gabapentin does not induce or inhibit hepatic mixed function oxidase enzymes responsible for drug metabolism, does not interfere with the metabolism of commonly coadministered antiepileptic drugs, and is minimally bound to plasma proteins.

Food has no effect on the rate or extent of absorption of gabapentin.

Table 1 summarizes the mean steady-state pharmacokinetic parameters of Neurontin capsules.

#### Table 1: Summary of Neurontin (gabapentin) Mean Steady-State Pharmacokinetic Parameters in Adults Following Q8H Administration

Pharmacokinetic Parameter	300 mg (N = 7)	400 mg (N = 11)
C <sub>max</sub> (µg/mL)	4.02	5.50
<sup>t</sup> max (hr)	2.7	2.1
t <sup>1</sup> / <sub>2</sub> (hr)	5.2	6.1
AUC(o-a) (µg•hr/mL)	24.8	33.3
AE% <sup>1</sup>	NA	63.6

<sup>1</sup> Amount excreted in urine (% of dose)

NA = Not available

In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid are approximately 20% of corresponding steady-state trough plasma concentrations.

#### Elderly:

Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in subjects under 30 years of age to about 125 mL/min in subjects over 70 years of age. Renal clearance (CLr) of gabapentin also declined with age; however, this decrease can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age-related compromised renal function (See Dosage and Administration).

#### **Renal Impairment:**

In patients with impaired renal function, gabapentin clearance is markedly reduced and dosage adjustment is necessary (See Table 5 in Dosage and Administration).

#### Hemodialysis:

In a study in anuric subjects (N=11), the apparent elimination halflife of gabapentin on non-dialysis days was about 132 hours; dialysis three times a week (4 hours duration) lowered the apparent half-life of gabapentin by about 60%, from 132 hours to 51 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (See Table 5 in Dosage and Administration).

#### Pediatric:

There are no pharmacokinetic data available in children under 18 years of age.

#### Hepatic Impairment:

Because gabapentin is not appreciably metabolized in humans, no study was performed in patients with hepatic impairment.

#### **Clinical Trials**

In placebo-controlled trials in patients not satisfactorily controlled with current antiepileptic drugs, Neurontin (gabapentin), when added to current antiepileptic therapy, was superior to placebo in reducing the frequency of both simple and complex partial seizures and secondarily generalized tonic-clonic seizures. Further analysis of data indicated a higher efficacy for complex partial seizures and secondarily generalized tonic-clonic seizures as compared to all seizure types. Doses ranged from 900 to 1800 mg/day, with a median dose of 1200 mg/day.

Long-term, open, uncontrolled studies in drug-resistant patients for periods of up to 18 months demonstrated that doses up to 2400 mg/day did not result in anything unusal in the type or frequency of adverse events.

#### INDICATIONS AND CLINICAL USE

Neurontin (gabapentin) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

#### CONTRAINDICATIONS

Neurontin (gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

#### PRECAUTIONS

General Neurontin (gabapentin) is not considered effective in the treatment of absence seizures and should therefore be used with caution in patients who have mixed seizure disorders that include absence seizures.

#### **Tumorigenic Potential**

Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rats, but not female rats or in mice, in oncogenic studies with doses of 2000 mg/kg which resulted in plasma concentrations 14 times higher than those occurring in humans at the maximum recommended dose of 2400 mg/day. The relevance of these pancreatic acinar cell tumours in male rats to humans is unknown, particularly since tumours of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer.

#### **Drug Discontinuation**

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When in the judgement of the clinician there is a need for dose reduction, discontinuation or substitution with alternative medication, this should be done gradually over a minimum of one week.

#### **Occupational Hazards**

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were somnolence, ataxia, fatigue and nystagmus. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that Neurontin does not affect them adversely.

#### Drug Interactions Antiepileptic Agents:

There is no interaction between Neurontin and phenytoin, valproic acid, carbamazepine, or phenobarbital. Consequently, Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the plasma

concentrations of gabapentin or the other antiepileptic drugs.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

#### **Oral Contraceptives:**

Coadministration of Neurontin with the oral contraceptive NorlEstrin<sup>+</sup> does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

#### Antacids:

Coadministration of Neurontin with an aluminum and magnesiumbased antacid reduces gabapentin bioavailability by up to 24%. Although the clinical significance of this decrease is not known, coadministration of similar antacids and gabapentin is not recommended.

#### Probenecid:

Renal excretion of gabapentin is unaltered by probenecid.

#### Cimetidine:

A slight decrease in renal excretion of gabapentin observed when it is coadministered with cimetidine is not expected to be of clinical importance.

#### Use in Pregnancy

No evidence of impaired fertility or harm to the fetus due to gabapentin administration was revealed in reproduction studies in mice at doses up to 62 times, and in rats and rabbits at doses up to 31 times the human dose of 2400 mg/day.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

#### Use in Lactation

It is not known if gabapentin is excreted in human milk, and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from gabapentin, breast-feeding is only recommended if the potential benefit outweighs the potential risks.

#### Use in Children

Systematic studies to establish safety and efficacy in children have not been performed. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that gabapentin was superior to placebo in reducing seizure frequency. Safety data showed that the incidence of adverse events in this group of patients were similar to those observed in older individuals.

#### Use in the Elderly

Systematic studies in geriatric patients have not been conducted. Adverse clinical events reported among 59 patients over the age of 65 years treated with Neurontin did not differ from those reported for younger individuals. The small number of individuals evaluated and the limited duration of exposure limits the strength of any conclusions reached about the influence of age, if any, on the kind and incidence of adverse events associated with the use of Neurontin.

As Neurontin is eliminated primarily by renal excretion, dosage adjustment may be required in elderly patients because of declining renal function (See Dosage and Administration).

#### Use in Renal Impairment

Gabapentin clearance is markedly reduced in this patient population and dosage reduction is necessary (See Table 5 in Dosage and Administration).

#### Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin. Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or other antiepileptic drugs.

For urinary protein determination the sulfosalicylic acid precipitation procedure is recommended, as false positive readings were reported with the Ames N-Multistix SG<sup>®</sup> dipstick test, when gabapentin or placebo was added to other anticonvulsant drugs.

#### ADVERSE REACTIONS

#### Incidence in Controlled Clinical Trials

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients with partial seizures participating in placebo-controlled studies. In these studies, either Neurontin (at doses of 600, 900, 1200 or 1800 mg/day) or placebo were added to the patient's current antiepileptic drug therapy

The most commonly observed adverse events associated with the use of Neurontin in combination with other antiepileptic drugs, not seen at an equivalent frequency in placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, nystagmus and tremor.

Among the treatment-emergent adverse events occurring in Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54, from one controlled study) experienced approximately a two-fold increase, as compared to patients on lower doses of 600 to 1200 mg/day (n=489, from several controlled studies), in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Adverse events were usually mild to moderate in intensity, with a median time to resolution of 2 weeks.

Since Neurontin was administered most often in combination with other antiepileptic agents, it was not possible to determine which agent(s) was associated with adverse events.

Table 2: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Add-On Trials (Events in at Least 1% of Neurontin Patients and Numerically More Frequent than in the Placebo Group)

BODY SYSTEM/ Adverse Event (AE)	Neurontin <sup>a</sup> N = 543 %	Placebo N = 378 %
BODY AS A WHOLE: Fatigue Weight Increase Back Pain Peripheral Edema	11.0 2.9 1.8 1.7	5.0 1.6 0.5 0.5
CARDIOVASCULAR: Vasodilatation	1.1	0.3
DIGESTIVE SYSTEM: Dyspepsia Dry Mouth or Throat Constipation Dental Abnormalities Increased Appetite	2.2 1.7 1.5 1.5 1.1	0.5 0.5 0.8 0.3 0.8
HEMATOLOGIC AND LYMPHATIC SYSTEMS: Leukopenia	1.1	0.5
MUSCULOSKELETAL SYSTEM: Myalgia Frocture	2.0 1.1	1.9 0.8
NERVOUS SYSTEM: Somnolence Dizziness Ataxia Nystogmus Tremor Nervousness Dysarthria Amnesia Depression Abnormal Thinking Twitching Abnormal Coordination	19.3 17.1 12.5 8.3 6.8 2.4 2.4 2.2 1.8 1.7 1.3 1.1	8.7 6.9 5.6 4.0 3.2 1.9 0.5 0.0 1.8 1.3 0.5 0.3
RESPIRATORY SYSTEM: Rhinitis Pharyngitis Coughing	4.1 2.8 1.8	3.7 1.6 1.3
SKIN AND APPENDAGES: Abrasion Pruritus	1.3 1.3	0.0
UROGENITAL SYSTEM: Impotence	1.5	1.1
SPECIAL SENSES: Diplopia Amblyopia	5.9 4.2	1.9 1.1
LABORATORY DEVIATIONS: WBC Decreased	1.1	0.5

<sup>a</sup> Plus background antiepileptic drug therapy

Data from long-term, open, uncontrolled studies shows that Neurontin treatment does not result in any new or unusual adverse events.

#### Withdrawal From Treatment Due to Adverse Events

Approximately 6.4% of the 543 patients who received Neurontin in the placebo-controlled studies withdrew due to adverse events. In comparison, approximately 4.5% of the 378 placebo-controlled participants withdrew due to adverse events during these studies. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue, nausea and/or vomiting and dizziness (all at 0.6%).

#### Other Adverse Events Observed in All Clinical Trials

Adverse events that occurred in at least 1% of the 2074 individuals who participated in all clinical trials are described below, except those already listed in the previous table:

Body As a Whole	÷.	aesthenia, malaise, facial edema
Cardiovascular System	1	hypertension
Digestive System	3	anorexia, flatulence, gingivitis
Hematologic and Lymphatic System	-	purpura; most often described as bruises resulting from physical trauma
Musculoskeletal System	1	arthralgia
Nervous System	ţ	vertigo, hyperkinesia, parasthesia, anxiety, hostility, decreased or absent reflexes
Respiratory System		pneumonia
Special Senses	8	abnormal vision

#### SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute, life-threatening toxicity has not been observed with Neurontin (gabapentin) overdoses of up to 49 grams ingested at one time. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patients clinical state or in patients with significant renal impairment.

Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, reduce taxicity from overdoses.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation

#### DOSAGE AND ADMINISTRATION

#### Adults

1

The usual effective maintenance dose is 900 to 1200 mg/day. Treatment should be initiated with 300 to 400 mg/day. Titration to an effective dose, in increments of 300 mg or 400 mg/day, can progress rapidly and can be accomplished over three days (see Table 3). Neurontin is given orally with or without food.

Table 5. Tirration Schedule				
DOSE	Day 1	Day 2	Day 3	
200 mg/day	300 mg OD	300 mg BID	300 mg TID	

Table 2 Titation Cohedula

Data from clinical trials suggest that doses higher than 1200 mg/day may have increased efficacy in some patients; however, higher doses may also increase the incidence of adverse events (See Adverse Reactions).

Daily maintenance doses should be given in three equally divided doses (See Table 4), and the maximum time between doses in a three times daily schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations in order to optimize Neurontin therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, Neurontin may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

#### Table 4. Maintenance Dosage Schedule

fotal Daily Dose (mg/day)	Schedule
900	300 mg TID
1200	400 mg TID
1800	2 x 300 mg TID
2400	2 x 400 mg TID

Dosage adjustment in elderly patients due to declining renal function and in patients with renal impairment or undergoing hemodialysis is recommended as follows:

#### Table 5: Maintenance Dosage of Neurontin in Adults With Reduced Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 Three times a day
30-60	600	300 Twice a Day
15-30	300	300 Once a Day
<15	150	300 Once Daily Every Other Day
Hemodialysis <sup>a</sup>	-	200-300 <sup>b</sup>

<sup>a</sup> Loading dose of 300 to 400 mg

<sup>b</sup> Maintenance dose of 200 to 300 mg Neurontin following each 4 hours of hemodialysis

#### Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900-1200 mg/day. Doses above 1200 mg/day have not been investigated.

#### AVAILABILITY OF DOSAGE FORMS

Neurontin (gabapentin) capsules are supplied as follows:

#### 100-mg capsules,

Hard gelatin SUPRO® capsules with white opaque body and cap printed with "PD" on one side and "Neurontin/100 mg" on the other. Bottles of 100 capsules.

#### 300-mg capsules,

Hard gelatin SUPRO\* capsules with yellow opaque body and cap printed with "PD" on one side and "Neurontin/300 mg" on the other. Bottles of 100 capsules.

#### 400-mg capsules,

Hard gelatin SUPRO® capsules with orange opaque body and cap printed with "PD" on one side and "Neurontin/400 mg" on the other. Bottles of 100 capsules.

#### Composition

Capsules contain gabapentin, lactose, corn starch, and talc. Capsule shells may contain gelatin, titanium dioxide, silicon dioxide, sodium lauryl sulfate, yellow iron oxide, red iron oxide, and FD&C Blue No. 2.

#### Stability and Storage Recommendations

Store at controlled room temperature 15-30°C.



... EASY TO HANDLE



PARKE-DAVIS Scarborough, Ontario, M1L 2N3 M. Warner-Lambert Company, Parke-Da ion, Warner-Lambert Canada Inc., auth. i



#### ticlopidine hydrochloride 250 mg tablets

#### THERAPEUTIC CLASSIFICATION Inhibitor of Platelet Function

ACTION Ticlid (ticlopidine hydrochloride) is an inhibitor of platelet aggregation. It causes a time and dose-dependent inhibition of platelet aggregation and release of platelet factors, as well as a prolongation of bleeding time. The drug has no significant in-vitro activity

The exact mechanism of action is not fully characterized, but does not involve inhibition of the prostacyclin/thromboxa pathways or platelet cAMP

Ticld interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect of Ticld on platelet function is irreversible.

Template bleeding time is usually prolonged by two-to five-fold of baseline values with the therapeutic dose of Ticlid. Upon discontinuation of Ticlid dosing, bleeding time and other platelet function tests return to normal within one week

in the majority of patients. The correlation between ticlopidine hydrochloride plasma levels and activity is still under investigation. Much of the follow-The correlation between tooplane patients corresponding to the age of patients barricipating in clinical triak (mean age 63 years). After oral administration of the therapeutic dose of Ticlid, rapid absorption occurs, with peak plasma levels occurring at approximately 2 hours after dosing. Absorption is at least 80% complete. Administration of Ticlid after meals results in an increased (20%) level of ticlopidine hydrochloride in plasma. Steady state plasma levels of ticlopidine hydrochloride in plasma.

with plasma drug levels

Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins in a nonsaturable manner.

saturation manner. Ticlopidien hydrochlonde is metabolized extensively by the lives no intact ticlopidine hydrochlonide is detected in the urine. Unmetabolized ticlopidine hydrochlonide is a manor component, in plasma after a single dose, but at steady state, ticlopidine hydrochlonide is the major component. Impaired hepatic function resulted in higher than normal plasma levels of unchanged ticlopidine hydrochlonide after

peptic user or intracrinal bleeding. 5. Severe liver dysfunction. WARNINGS The following warnings were developed from clinical trial experience with over 2000 patients with cerebroxacular disease who were freated with fidopidine for as long as 5.8 years. Hematological Complications: About 2.4% of ticlopidine-treated patients in clinical trials developed neutropenia (defined as an absolute neutrophil count (ANC) below 1.2 x 10<sup>6</sup> cells/b). The incidence of severe neutropenia (ANC-0.45 x 10<sup>6</sup> cells(t)) was 0.8%, severe neutropenia occurs during the first 3-12 weeks of therapy, and may develop quickly over a few days. The bone marrow shows a reduction in mycolid precursors. The condition may be life-threatening. It is usually reversible, and the recovery occurs within 1-3 weeks after discontinuation of the drug but may take longer on occasion.

becepting it is usually reversible, and the recovery occurs within 1–3 weeks after discontinuation of the drug but may take longer, on occasion. In clinical triads, thrombocytopenia (defined as a platelet count of -0.8 x 10<sup>11</sup> cells/L) has been observed in 0.4% of ticipodine patients. The incidence of thrombocytopenia in patients on ASA or placebo was 0.3% or 0.4% nespectively. The thrombocytopenia may occur as an isolated finding or in combination with neutropenia. Thrombocytopenia occurs during the inst 3-12 weeks of therapy, and recovery usually occurs atter drug discontinuation. All patients should have a white blood cell count with a differential and platelet count performed every 2 weeks starting at baseline, before treatment is initiated, to the end of the third month of therapy with Ticld. When the neutrophil counts of the drug obstrained weeks at the resonance of the other should be continued. Because of the low 30% of the baseline, the value should be discontinued. Ticld of any reason within the first 90 days have an additional CBC with white cell differential court obsorpenia, daves after discontinuation of therapy. (See PEECAUTIONS) All forms of hematological adverse reactions are potentially fall. Rarely, cases of pancytopenia, aplastic anemia or thrombocytopenia, therefore cateful attention to diagoosis should be materoported. Therefore, therapy therefore, therefore, and attention to diagoosis should be made to guide treatment, platest transfusion may be harmful in these patients.

may be narmful in these patients. Hemorrhagic Complications: Prolongation of bleeding time occurs in subjects treated with Ticlid. Purpura and a few case of more serious hemorrhagic events such as hematemeats, melera, hemothorax and intracranial bleeding thase been reported. Patients must be instructed to watch for signs of bleeding disorders and to report any abnormality to their physican immediately. Told therapy has to be stopped by the patient if a physican is not immediately available for consultation. Anticoagulant Drugs: Should be avoided as tolerance and safety of simultaneous administration with Ticlid has not. hematic Abnormality. Lot of the provided as tolerance and safety of simultaneous administration with Ticlid has not.

been established. Hepatic Abnormalities: Most patients receiving ticlopidine hydrochlonde showed some increase of their alkaline phosphatase values above their baseline and in one-third the increase exceeded the upper reference range. In 696 the value was greater than twice the upper reference range. These increases in alkaline phosphatase were nonprogressive and asymptomatic. In clinical trans, two cases (OLIMs) of choicetaic juandice accompanied by elevated transminase alkaline phosphatase, and bilirubin levels above 43 µmol/L have been observed. Both patients recovered promptly upon drug discontinuation

Pregnancy: The safety of Ticlid in pregnancy has not been established. It should not be used in pregnant patients Pediatric Use: Safety in children has not been studied. Do not use in pediatric patients.

#### PRECAUTIONS

PRECAUTIONS Selection of Patients: Ticlid should be used only for the established indications (see INDICATIONS) and should put be given to patients with haematopoietic disorders, haemostatic disorders, patients suffering from conditions associated with active bleeding (see CONTRAINDICATIONS) and patients anticipating elective surgery. In clinical trails elderly patients tolerated the drug well, but safety in children and pregnant women has not been established. Clinical Monitoring: All patients have to be carefully monitored for clinical signs and symptoms of adverse drug reactions (see ADVERSE REACTIONS). The signs and symptoms possibly related to neutropenia (teer, thills, sore throat,

ulcerations in oral cavity), thrombocytopenia and abnormal hemostasis (prolonged or unusual bleeding, bruising, purpura, dark stool), jaundice (including dark urine, light coloured stool) and allergic reactions should be explained to

purpura, dark stool), jaundice (including dark urine, light coloured stool) and allergic reactions should be explanee to the patients who should be advised to stop medication and consult their physician immediately if any of these occur. **Laboratory Monitoring:** All patients should have a white blood cell count with a differential and a platelet count performed every 2 weeks starting at baseline, before treatment is initiated, to the end of the third month of therapy with Tcild. When the neutrophil count shows a declining trend or the neutrophil numbers have failen below 30% of the baseline, the value should be confirmed. If the presence of neutropenia (ANC <1.2 x 10<sup>o</sup> cells/L) or thrombocytopenia (< 0.8 x 10<sup>-11</sup> cells/L) are confirmed, the drug should be discontinued. Because of the long plasma half-life of Ticklid, it is recommended that any patient who discontinues Ticklid for any reason within the first 90 days, have an additional CBC with white cell differential obtained two weeks after discontinued in of therapy (see WARNINGS). Thereafter, the WBC counts medical be presented for promoting or given supressition of metropenia.

counts need only be repeated for symptoms or signs suggestive of neutropenia. Liver function tests should be conducted during therapy with Ticlid (ticlopidine hydrochloride) in response to signs and

symptoms suggestive of hepatic dysfunction. Elective Surgery: Ticlid should be discontinued 10 to 14 days prior to elective surgery or dental extraction and bleeding time and thrombocyte count performed before the procedure if clinically indicated.

bleeding time and thrombocyte count performed before the procedure it clinically indicated. **Emergency Surgery:** Prohonged bleeding during surgery may be a problem in biologichine-treated patients. Transfusions of fresh platelets would be expected to improve haemostasis in such patients, but there are no data from clinical trials to confirm this expectation. There are data from clinical pharmacology trials that indicate treatment with glucocorticosteroids can normalize bleeding time in ticlopidine-treated subjects, but there is no experience with ticlopidine-treated surgical patients to show that such treatment improves haemostasis. **Specific Precautions: Liver:** Ticlid is contraindicated in patients with severe liver dysfunction or cholestatic jaundice.

Mild increase of alkaline phosphatase may be seen for the duration of the treatment and is inconsequential in the majority of patients (see WARNINGS and CONTRAINDICATIONS). **Kidneys:** Ticlid has been well tolerated in patients with moderately decreased renal function. In severe renal disease

aution and close monitoring are recommended.

Castrointestinal system: Conditions associated with active bleeding, such as bleeding ulcers, constitute contraindication for Ticlid. Clinical judgement and monitoring of stool for occult blood are required for patients with a history of ulcerative lesions

Trauma: Ticlid should be discontinued temporarily until the danger of abnormal bleeding is eliminated. A single fatal case of intracranial bleeding following head trauma has been reported. The extent to which Ticlid may have contributed to the severity of the bleeding is unknown. Drug Interactions: Since ticlopidine is metabolized by the liver, dosing of (Ticlid) or other drugs metabolized in the

The following table outlines the agents which have been concomitantly administered with ticlopidine hydrochloride and

OBSERVED INTERACTION
Ticlopidine potentiates the effect of ASA or NSAIDs on platelet aggregation. The safety of use of ticlopidine with ASA or NSAIDs is not established.
30% increase in t <sup>1</sup> / <sub>2</sub> of antipyrine.
Dose of products metabolized by hepatic microsomal enzymes to be adjusted
when starting or stopping concomitant therapy with ticlopidine hydrochloride.
t <sup>1</sup> / <sub>2</sub> of theophylline increased from 8.6 to 12.2 hr along with a comparable reduction in its total plasma clearance.
Approximately 15% reduction in digoxin plasma levels (little or no change in digoxin's efficacy expected).
Chronic administration of cimetidine induced a 50% reduction in clearance of a single dose of ticlopidine hydrochloride.
20% decrease in ticlopidine plasma level when administered after antacids.

Phenolabilital
No interaction reported,
No in

adverse interactions. ADVERSE REACTIONS Most adverse effects are mild; transient and occur early in the course of treatment. In controlled clinical trials of 1 to 5 years duration, discontinuation of Ticlid (ticlopidine hydrochloride) due to one or more adverse effects was required in 20.9% of patients. In these same trials, ASA and placebo led to discontinuation in 14.5% and 6.7% of patients respectively. The incidence rates of adverse reactions listed in the following table were derived from multicenter, controlled dinical trials comparing ticlopidine HCI, placebo, and ASA over study periods of up to 5 years. The rates are based on adverse reactions considered pirobably drug-related by the investigator. Adverse experiences occurring in greater than one percent of patients treated with Ticlid in controlled clinical trials are shown in the Table below. **PERCENT OF PATIENTS IN CONTROLLED STUDIES** 

	Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence		Ticlid (n=2048) Incidence	ASA (n=1.527) Incidence	Placebo (n=536) Incidence
Event	1020 C 17 C 1	N 34	1000 100	NY 43.1	49.4 12.00	麗 / 慶	
Diamhea	12.5(6.3)*	5.2(1.8)	4.5(1.7)	Nausea	7.0(2.6)	6.2(1.9)	4.7(0.9)
Dyspepsia	7.0(1.1)	9.0(2.0)	0.9(0.2)	Rash	5.1(3.4)	1.5(0.8)	0.6(0.9)
GIPain	3.7(1.9)	56(27)	1.3(0.4)	Neutropenia	2.4(1.3)	0.8(0.1)	1.4(0.4)
Purnaira	2.2(0.2)	1.6(0.1)	0.0(0.0)	Vomiting	1.9(1.4)	1.4(0.9)	0.9(0.4)
Flatulence	1.5(0,1)	1.4(0.3)	0.0(0.0)	Pruritus	1.3(0.8)	0.3(0.1)	0.0(0.0)
Dizziness	1.1(0.4)	0.5(0.4)	0.0(0.0)	Anorexia	1.0(0.4)	0.5(0.4)	0.0(0.0)

Percent of patients (in parentheses) discontinuing clinical trials due to event.
 The incidence of thrombocytopenia in these controlled studies was 0.4% in the Ticlid and placebo groups of patients

The incidence of thrombocytopenia in these controlled studies was 0.4% in the Ticlid and placebo groups of patients and 0.3% in the ASA patient population. The following rare events have been reported and their relationship to Ticlid is uncertain. Pancytopenia, hemolytic memia with relaciologycosis, thrombocytopenic thromboticpurpura, jaundice, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepathis, nephrotic syndrome, myositis, anajoederna, lever, hyponatremia, bleeding increased (spontaneous) post-traumatic or postoperative, (hotestatic jauncice, colitis, exprtmen multitorme, hepatic necrosis, hepatocellular jaundice, peptic dice, Stevens-Johnson syndrome, renal failure, and sepsis. **Gastrointestinal:** Ticlid therapy has been associated with a variety of gastrointestinal complaints including diarthea and mauses. The majority of cases are mild and transient in nature and occur within 5 minitation of therapy. Typicality, events are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued.

Interaction of the discontinued. Hemorrhagic: Ticli has been associated with a number of blesding complications such as ecolymosis, epistaxis, hematuna, conjunctival hemorrhage, gistrointestinal bleeding, and postoperative bleeding. Intraceredral bleeding was rate in clinical tids with Ticlid, and was no more than that see with comparator agents (ASA placebo). Rash: Tclopidine hystochioode has been associated with a maculopapular or utricanial ratk (often with pruntus), Rash traceredral bleeding was rate in clinical tids with Ticlid, and was no more than that see with comparator agents (ASA placebo). Rash: Tclopidine hystochioode has been associated with a maculopapular or utricanial ratk (often with pruntus), Rash togally occurs within 3 months of initiation of therapy, with a mean time to orate of 11 days. If drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of more sever rashes. Attered Laboratory Findings: Hematological: Agranulocytosis, eosinophilia, neutropenia, pancytopenia, thrombocytopenia, and thrombocytosis have been associated with relevations of alkaline phosphatase (See WARNINGS). Maximal changes occur within 1-4 months of therapy with intonin, SCOT, SCPT, and CGTP. Cholesterol: Chronic Ticlid therap has been associated with increased 8-10% after 1-4 months of therapy. Not unther progressive of HDL-C; LD-C, VLD-C, and tragvendes are increased 8-10% after 1-4 months of therapy. Not thirther progressive of WDL-C; LD-C, VLD-C, and tragvendes are increased 8-10% after 1-4 months of therapy. The ratios of the lipoprotein subfractions are unchanged. The effect is not correlated with age, sex, alcohol use, or diabetes.

correlated with age, sex, alcohol use, or diabetes. SYMPTOMS AND TREATMENT OF OVERDOSAGE One case of deliberate overdosage with Ticlid (ticlopidine SYMPTOMS AND TREATMENT OF OVERDOSAGE One case of deliberate overdosage with Ticlid (ticlopidine hydrochloride) has been reported in a foreign postmarketing surveillance program. A 38-year-oid maie took a single 6000 mg dose of Ticlid (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Based on animal studies, overdosage may result in severe gastrointestinal intolerance. In the case of excessive bleeding after injury or surgery, standard supportive measures should be carried out if indicated, including gastric lavage, platelet transfusion and use of corticosteroids. DOSAGE AND ADMINISTRATION The recommended dose of Ticlid (ticlopidine hydrochloride) is 250 mg twice daily with food. Ticlid should be taken with meals to minimize gastrointestinal intolerance.

#### PHARMACEUTICAL INFORMATION (t) Drug Subst

Description: Ticlopidine hydrochloride is a white crysfalline solid, It is freely soluble in water and self buffers to a pH of 3.6. It also dissolves freely in methanol, is sparingly soluble in buffer solutions above pH 6.0, methylene chloride and ethanol, and is slightly soluble in acetone.

ernanou, and is signity soluble in acetone. (ii) Composition: Ticlopidime hydrochloride tablets are provided, as white film coated tablets containing ticlopidime hydrochloride, citric acid, povidone, micro-crystalline cellulose, corn starch, stearic acid powder, magnesium stearate and water. The coating suspension consists of hydroxypropyl methylcellulose, titanium dioxide and phyethylene glycol. The ink for printing contains FDAC blue #1 aluminum lake. (iii) Stability and Storage Recommendations: Store at room temperature. Ticlid tablets should be dispensed in light

existant containers. Blister packs should not be exposed to light. **AVAILABILITY** Ticlid 250 mg tablets are oval white film coated tablets printed using blue ink with Ticlid above half an arrow on one side, "250" above half an arrow on the other side. The tablets are available in fold-over cards of

arrow on one side, 250 adove han an another on the other side. The tables are available in role of 28 tablets (2 blisters of 14 tablets) and 56 tablets (4 blisters of 14 tablets). For the first 3 months of therapy, only request or dispense the 14 days supply of tablets (see PRECAUTIONS). Product Monograph available to Health Professionals on request.

Roche



Hoffmann-La Roche Limited, Mississauga, Ontario L5N 6L7

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(sumatriptan succinate) 100 mg Tablet 6 mg Subcutaneous Injection and Autoinjector THERAPEUTIC CLASSIFICATION Migraine Therapy PHARMACOLOGIC CLASSIFICATION 5-HT -like Recentor Agonist CLINICAL PHARMACOLOGY

IMITREX (sumatriptan succinate) is a selective 5-hydroxytryptamine<sub>1</sub>-like (5-HT<sub>1</sub>-like) receptor agonist which has been shown to be effective in relieving migraine headache. The activity of sumatriptan at the 5-HT\_1-like receptor mediates a selective vasoconstriction within the cardid arterial inclutions a selective vacuation and within the cardid arterial circulation supplying the intracranial and extracranial tissues such as the brain and meninges. The dilatation of cranial blood vessels is thought to play an important role in the underlying mecha-nism of migraine. Sumatriptan (0.01-100 µM) caused a dose-dependent vasoconstriction in human isolated perfused dura mater as judged by increases in perfusion pressure. The activation of 5-HT1-like receptor by sumatriptan suggests the possibility that the mechanism of the anti migraine action of sumatriptan could involve vasoconstriction of dural blood vessels. Sumatriptan has no effect at either 5-HT<sub>2</sub> or 5-HT<sub>3</sub> receptor subtypes. Clinical response begins 10-15 minutes following subcutaneous injection and around 30 minutes following oral adminis tration

Cardiovascular Effects: In vitro studies in human isolated epicardial coronary arteries suggest that the predominant contractile effect of 5-HT is mediated via 5-HT<sub>2</sub> receptors. However, 5-HT<sub>1</sub>-like receptors also contribute to some degree to the contractile effect seen. Transient increases in systolic and diastolic blood pressure (up to 20 mmHg) of rapid onset (within minutes), have occurred after intravenous administration of up to 64  $\mu$ g/kg (3.2 mg for 50 kg subject) to healthy volunteers. These changes were not dose related and returned to normal within 10-15 minutes. Following oral administration of 200 mg, however, mean peak increases in blood pressure were smaller and of slower onset than after intravenous or subcutaneous administration.

administration. Pharmacokinetics: Sumatriptan is repidly absorbed after oral and sub-cutaneous administration with a mean bioavailability of 96% after sub-cutaneous dosing and 14% after oral dosing. The low oral bioavailability is mainly due to hepatic metabolism and, to a lesser extent, to incom-plete absorption. The oral absorption of sumatriptan is not significantly affocted either during migraine attacks or by food. Following an oral dose of 100 mg, a mean Carsol 54 ng/m, was attained, while the time to peak plasma level was variable (0.5- 5 hours). However, 70% to 80% of Cmsx values were attained within 30-45 minutes of oral dosing. The mean plasm ball-life was approximately 2 hours; france 1.9 - 22 hours). mean plasma half-life was approximately 2 hours (range 1.9 - 2.2 hours). Following a 6 mg subcutaneous dose (standard injection) in the deltoid region of the arm or thigh or autoinjection into the thigh, a mean Case value of 60 ng/mL was attained at approximately 15 minutes. Mean plasma half-life was approximately 2 hours (range 1.7-2.3 hours). Sumatriptan is extensively metabolised by the liver and cleared to a lesser extent by renal excretion. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the unious aced acid analogue of sumatriptan is mainly excreted in the union where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no knownSHT, or SHT, activity. Minor metabolites have not been identified. Plasma protein binding of sumatriptan in humans is low (14%-21%). No differences have been observed between the pharma-cokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 years old).

INDICATIONS AND CLINICAL USES: IMITREX (sumatriptan succinate) is indicated for the relief of migraine attacks with the solution of the relief of migraine attacks with the vibility area. Sumatripten is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic basilar migraine. **CONTRAINDICATIONS:** MINTRX (sumatriptan succinate) is contraindicated in patients with known hypersensitivity to any of the components of

Ladd in padents with Alwin Hyperbandstrowy of any of the components of the formulation. Sumatriptan is contraindicated in patients with ischaemic heart disease, angine pectoris including Prinzmetal angine (conary vasospasm), previous myocardial infarction and uncontrolled hypertension. Sumatriptan is also contraindicated in patients taking ergotamine-containing preparations. Until further data are available, the use of sumatriptan is contraindicated in patients with hemiplegic migraine, basilar migraine and in patients receiving treatment with MAOI's, selective 5-HT reuptake inhibitors and lithium.

#### WARNINGS

There is no experience in patients with recent cerebrovascular accidents or cardiac arrhythmias (especially tachycardias). Therefore, the use of IMITREX (sumatriptan succinate) in these view of the second seco patients is not recommended.

Sumatriptan has been associated with transient chest pain and tight-ness which may mimic angina pectoris and may be intense. Only in rare cases have the symptoms been identified as the result of coronary vasospasm. The vasospasm may result in arrythmia, ischaemia or myocardial infarction. If the patient experiences symptoms which are sovero or presistent and are consistent with angine, appropriate inves-tigations should be carried out to check for the possibility of ischaemic changes. A careful medical history should be taken before sumatriptan is prescribed to exclude pre-existing cardiovascular disease. Sumatripten should be used with caution in patients in whom there is a concern of ischeemic heart disease, as well as in patients with arte-riosclerotic diseases such as peripheral and/or carebral vascular dis-ease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fbrillation, ventricular fibrillation, ventricu-lar tachycardia and myocardial infarction, as well as transient ischeemic ST wave elevations associated with IMITREX injection. Consideration should be given to administering the first dose of Imitrax injection in the physician's office to patients in whom unrecognised coronary artery disease is comparatively likely: postmenopausal women, males over 40, patients with risk factors for CAO (hypertension, hypercholesterolaemia, obesity, diabetes, smoking, or strong family his-tory of CAO). Sumatriptan injection should not be exceeded. Sumatriptan should be used with caution in patients in whom there is a The recommended dose of sumatriptan should not be exceeded.

#### PRECAUTIONS

Cluster Headache: There is insufficient information on the efficacy and safety of sumatriptan in the treatment of cluster headache, which is pre-sent in an older, predominantly male population. The need for prolonged use and the demand for repeated medication in this condition renders the dosing information inapplicable for cluster headache. General: Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan can be taken following any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hours have elapsed following sumatriptan administration. Chest, jaw or neck tightness is relatively common (3-5% in controlled clinical trials) after IMITREX injection, but has only been rarely associated with ischaemic ECG changes. Sumatriptan may cause a short-lived elevation of blood pressure [see Clinical Pharmacology and Contraindications]. Patients should be cautioned that drowsiness may occur as a result of treatment with sumatriptan. They should be advised not to perform skilled tasks eg. driving or operating machinery if drowsiness occurs.

Hepatic and Renal Impairment: The effects of renal and hepatic impairment on the efficacy and safety of sumatriptan have not been evaluated. Therefore sumatriptan is not recommended in this patient population.

Use in Elderly (>65 years): Experience of the use of sumatriptan in patients aged over 65 years is limited. Therefore the use of sumatriptan in patients over 65 years is not recommended.

Use in Children (<18 years): The safety and efficacy of sumatriptan in children has not been established and its use in this age group is not recommended.

Use in Pregnancy: Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or post-natal development due to sumatriptan. Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervice thoracic blood vessel configuration in the fetuses. These effects were only seen at the highest dose tested, which affected weight gain in the dams, and at which blood levels were in excess of 50 times those seen in humans after theraneutic doses. A direct association with sumatriptan treatment is considered unlikely but cannot be excluded. Therefore, the use of sumatriptan is not recommended in pregnancy.

Lactation: Sumatriptan is excreted in breast milk in animals. No data exists in humans, therefore, caution is advised when administering sumatriptan to nursing women.

Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propanolol, flunar-izine, pizotifen or alcohol. Multiple dose interaction studies have not been performed

ADVERSE REACTIONS: The most common adverse reaction associated with IMITREX (sumatriptan succinate) administered subcutaneously is transient pain (local erythema and burning sensation) at the site of injection. Other side effects which have been reported for both the oral and subcutaneous routes, but were more common for the subcutaneous route, include sensations of tingling, heat, heaviness, pressure or tightness in any part of the body, chest symptoms, flushing, dizziness and feelings of weakness. Transient increases in blood pressure arising soon after treatment have been recorded. Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery discorollary vasopsim in patients with a natury of corollary variety of ease, known to be susceptible to coronary artery vasopsim, and, very rarely, without prior history suggestive of coronary artery disease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricul-lar tachycardia, myocardial infarction, and transient ischaemic ST elevation associated with IMITREX injection (see WARNINGS).

	Tablote	Placabo	S.C.	Placabo
Event	N=1456	N=296	N=2665	N=868
Controlatestingh				
nauseabromiting	12%	4%	8%	45
nausea/volinility	12.70	4/0	0.0	4 /0
abdominal discomfort	1%	<1%	195	~185
dysohagia	185	0%	185	0%
gastro-oesophageal reflux.	, , , ,	0.0		070
diarrhea and abnormal stools	<1%	≤1%	<1%	0%
Neurological:				
tingling	1%	<1%	9%	2%
malaise/fatioue	8%	2%	2%	<155
dizziness/vertigo	5%	2%	8%	3%
warm/hot sensation	155	<1%	8%	3%
burning sensation	<1%	0%	5%	<1%
numbness	195	<1%	3%	1%
drowsiness/sedation	3%	<1%	2%	<1%
paresthesia	1%	0%	1%	<1%
Cardiovascular:				
flushing	<1%	1%	5%	2%
hypertension, tachycardia	<1%	0%	<1%	<1%
bradycardia	<1%	0%	<1%	0%
palpitations	<1%	<1%	<1%	<1%
hypotension	<1%	0%	<1%	<155
pallor	<1%	0%	<1%	0%
pulsating sensation	<1%	0%	<1%	<1%
Symptoms of Potentially				
Cardiac Origin:				
neck pain/stiffness	2%	0%	3%	<1%
feeling of heaviness	3%	<1%	8%	1%
pressure sensation	1%	<1%	6%	1%
chest symptoms (including				
chest pain)	3%	<1%	4%	<1%
throat symptoms (including				
sore or swollen throat or				
throat spasms)	2%	0%	2%	<1%
Musculoskeletai:				
weakness	3%	<1%	3%	<1%
myalgia	2%	0%	1%	<1%
feeling of tightness	<1%	0%	3%	<1%
joint symptoms, backache,				
muscle stiffness or cramp	<1%	0%	0%	0%
Miscellaneous:				
sweating	2%	<1%	2%	<1%
disorder of mouth and tongue	2%	<1%	4%	2%
disturbance of hearing	<1%	0%	<1%	0%
visual disturbance	<1%	0%	<1%	<1%

Fatigue and drowsiness have been reported at slightly higher rates for the oral route, as were nausea and vomiting; the relationship of the latter adverse reactions to sumatriptan is not clear. The preceding table lists the incidence of adverse reactions reported in clinical trials undertaken with the oral formulation and the subcutaneous injection. Most of the events were transient in nature and resolved within 45 min-utes of subcutaneous administration and 2 hours of oral administration. Minor disturbances of liver function tests have occasionally been observed. There is no evidence that clinically significant abnormalities

occurred more frequently with sumatriptan than with placebo. SYMPTOMS AND TREATMENT OF OVERDOSE

There have been no reports of overdosage with IMITREX (sumatriptan succinate). Experience with doses outside of the recommended labelling is as follows: One patient received two 6 mg subcutaneous doses within 30 minutes and one patient received four 100 mg tablets within 24 hours, with no adverse events. If overdosage with sumatrip-tan occurs, the patient should be monitored and standard supportive treatment applied as required. Toxicokinetics are not available. The effect of haemodialysis or peritoneal dialysis on the serum concentra-

# tion of sumatriptan is unknown. DOSAGE AND ADMINISTRATION

General: IMITREX (sumatriptan succinate) is indicated only for the intermittent treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally or subcutaneously. Sumatriptan is equally effective when administered at any stage of a migraine attack, however, it is recom-mended that sumatriptan be given as early as possible after the onset of auro or headache. Clinical response begins 10-15 minutes following subcutaneous injection and around 30 minutes following oral administration. Further doses of sumatriptan should not be taken if the patient shows no response to the initial treatment of a single attack. However, shows no response to the initial treatment of a single attack. However, analgesic medication other than ergotamine-containing preparations may be used for further pain relief. Sumatriptan may be taken for sub-sequent attacks. Twenty-four hours should elapse before sumatriptan is taken following any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hours have elapsed following sumatriptan administration. **TABLETS:** The recommended adult dose of IMITREX Tablets is a single 00 ms tablet. Clinical tripte hour observe that angregation that angregation that and the single tablet.

100 mg tablet. Clinical trials have shown that approximately 50-75% of patients have headache relief within two hours after oral dosing, and that a further 15-25% have headache relief by 4 hours. If a patient has not responded within 4 hours, he/she is considered to be a nonresponder. Rescue medication excepting ergotamine-containing preparations may be used. Patients who have had a successful preparations may be used. Fatients who have had a successful response (i.e. no pain or mild pain) may treat a latter recurrence of headache with an additional 100 mg dose of sumatriptan. The maxi-mum dose in 24 hours is  $3 \times 100$  mg tablets (300 mg). Patients who do not respond to the first dose should not take a second dose of suma-triptan for the same attack. Sumatriptan may be taken for subsequent attacks. The tablet should be swallowed whole with water, not crushed or chowned

INJECTION: IMITREX Injection should be injected subcutaneously (on the outside of the thigh) using an autoinjector. The recommended adult dose of sumatriptan is a single 6 mg subcutaneous injection. Clinical trials have shown that patients continue to improve for at least 120 minutes after a single subcutaneous injection of sumetripan. If a patient utes after a single subcutaneous injection of sumetripan. If a patient has not responded within 2 hours, he/she is considered to be a non-responder. Rescue medication excepting orgotamine-containing preparations may be used. Patients who have had a successful response (ie. no pain or mild pain) may treat a later recurrence of headache with one additional 6 mg dose of sumatriptan, provided 1 hour has elapsed since the first dose. This 1 hour interval is based on the knowledge of the pharmacokinetics of the drug. The maximum dose

the knowledge of the pharmacoknetics of the drug. The maximum dose in 24 hours is two 6 mg injections (12 mg). Patients who do not respond to the first dose should not take a second dose of sumatriptan for the same attack. But, sumatriptan may be taken for subsequent attacks. STABILITY AND STORAGE RECOMMENDATIONS: IMITREX Tablets should be stored at 15°C to 30°C. IMITREX Injection should be stored between 2°C and 30°C and protected from light. AVAILABILITY OF DOSAGE FORMS: IMITREX isymatriptan succinate)

Tablets are pink, film-coated tablets available in blister packs contain-ing 6 tablets, packed in a cardboard carton. Each tablet contains 100 mg sumatriptan (base) as the succinate salt. IMITREX Injection is available in prefilled syringes containing 6 mg of sumatriptan base, as the succinate salt, in an isotonic solution (total volume = 0.5 mL). Syringes are placed in a tamper-evident carrying/disposal case. Two refilled stringes of a subtiniestre car acked in a patient terror prefilled syringes plus an autoinjector are packed in a patient starter kit. A refill pack is available containing 2 prefilled syringes in a carton. IMITREX Injection is also available to physicians or hospitals in a single dose vial (total volume = 0.5 mL) containing 6 mg of sumatriptan base as the succinate salt.

as the succinate sait. Imitrex<sup>2</sup> is a registered trade mark of Glaxo Group Limited, Glaxo Canada Inc. licensed use. Product Monograph available to physicians and pharmacists upon request. Please contact Glaxo Canada Inc., 7333 Mississauga Road N, Mississauga, Ontario, L5N GL4. **References:** 1. Edmeads J et al. Impact of migraine and tension-type headache on lifestyle, consulting behaviour, and medication use. A Canadian population survey. *Can J Neurol Sci 1937;20:131-137.* Schoneno L et al. Selftreatment of argute migraine with subruta.

Canadian population survey. *Can J Neurol Sci 1993;20:131-137.* 2. Schoenen J et al. Self-treatment of acute migraine with subcuta-neous sumatriptan using an auto-injector device: Comparison with customary treatment in an open, longitudinal study. *Cephalalgia* 1994;14:55-63 3. Product Monograph of IMITREX<sup>3</sup>, Glavo Canada Inc., 1993. 4. The Oral Sumatriptan International Multiple-Dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. *Eur Neurol* 1991;31:306-313. 5. The Sub-cutaneous. Tomatriptan International Study Econe. Treatment of cutaneous Sumatriptan International Study Group, Treatment of migraine attacks with sumatriptan. N Engl J Med 1991;325:316-321. 6, Sands GH. A protocol for butalbital, espirin and caffeine (BAC) detox-ification in headache patients. Headache 1990;30:491-495. 7. Tansey Intraction in headache patients. Headache 1990;30:491-496. 7. Iansey MJB et al. Long-term experience with sumatriptan in the treatment of migraine. Eur Neurol 1993;33:310-315. 8. Sullivan JT et al. Psycho-activity and abuse potential of sumatriptan. Clin Pharmacol Ther 1992;55:265-642. 9. Saltonen R. The time to onset and duration of adverse events reported after the acute treatment of migraine with sumatriptan. The 2nd International Conference European Headache Federation. June 15-18, 1994. Abstract from papers presented. Liege, Belgium. 10. Data on file. Glaxo Canada Inc., 1994. 11. Angus Reid Eventor 1994. 22. Voision in Marchan Schweime, Sweith, Data and Inc. Clave Schwarz, 1994. 2014. Research, 1994. 12. Variation in Migraine Severity. Data on file. Glaxo Canada Inc., 1994.





# amicta

(25, 100, 150 mg)

Antiepilepite ACTION AND CLINICAL PHARMACOLOGY LAMICTAL (amotrigine) is a drug of the phenythrazine dass chemically unrelated to existing antiepilepite drugs (AEDs). Lamotrigine is thought to act at votage-sensitive sodium channels to stabilize neuronal membranes and inhibit the canonigne is wrong in to ad a voltage service south in claimes to statute neuronal membranes and infinite the release of excitatory amino acid neurotransmitters (e.g. glutamate, aspartate) that are thought to play a role in the generation and spread of epileptic seizures. Clinical Trials

Clinical trais in placebo-controlled clinical studies, LAMICTAL has been shown to be effective in reducing seizure frequency and the number of days with seizures when added to existing antiepilepic drug therapy in adult patients with partial seizures, with or without generalized tonic-clonic seizures, that are not satisfactorily controlled. Pharmacokinetics

Pharmacokinetics Adults: LAMICTAL is rapidly and completely absorbed following oral administration, reaching peak plasma concentra-tions 1.4 to 4.8 hours ( $T_{max}$ ) post-dosing. When administered with food, the rate of absorption is slightly reduced, but the extent remains unchanged. Following single LAMICTAL doses of 50 - 400 mg, peak plasma concentration ( $T_{max}$ .O.6 + 6.4 µg/mL) and the area under the plasma concentration-versus-time curve (AUC-29.9 - 211 h + µg/mL) increase linearly with dose. The time-to-peak concentration, elimination half-life ( $t_{10}$ ) and volume of distribution (VdF) are independent of dose. The time-to-peak concentration, elimination half-life ( $t_{10}$ ) and volume of distribution (VdF) are independent of dose. The time-to-peak concentration, elimination half-life ( $t_{10}$ ) and volume of distribution (VdF) are independent of dose. The time-to-peak concentration, elimination half-life ( $t_{10}$ ) and volume of distribution (VdF) are independent of dose. The time-to-peak concentration and the range of 23%. In a single-doses study where healthy volunteers were administered both oral and intravenous doses of lamotrigine, the absolute bioavailability of oral lamotrigine was 98%.

Lamotrigne was 90%. Lamotrigne is approximately 55% bound to human plasma proteins. This binding is unaffected by therapeutic concentrations of phenytoin, phenobarbital or valproic acid. Lamotrigine does not displace other antiepileptic drugs (carbamazepine, phenytoin, phenobarbital) from protein binding sites. Lamotrigne is metabolized predominantly in the liver by glucuronic acid conjugation. The major metabolite is an inactive 2-N-glucuronide conjugate that can be hydrolyzed by *B*-glucuronidase. Approximately 70% of an oral LAMICTAL does is recovered in urine as this metabolite.

LAMICTAL dose is recovered in time as this metabolite. Elderly: The pharmacokinetics of lamotrigine in 12 healthy elderly volunteers. (≥ 65 years) who each received a single oral dose of LAMICTAL (150 mg) were not different from those in healthy young volunteers. (However, see PRECAUTIONS, Use in the Elderly, and DOSAGE AND ADMINISTRATION) Renal Impairment: The pharmacokinetics of a single oral dose of LAMICTAL (100 mg) were evaluated in 12 individu-als with chronic renal failure (with mean creatinine dearance of 13 mL/min) who were not receiving other antiepilepic drugs. In this study, the elimination half-life of unchanged lamotrigine was prolonged (by an average of 63%) relative to individuals with normal renal function (see PRECAUTIONS, Renal Failure and DOSAGE AND ADMINISTRATION). Hemodialysis: In six hemodialysis patients, the elimination half-life of unchanged lamotrigine was doubled off dialysis, and reduced by 50% on dialysis, relative to individuals with normal renal function. Hepatic Impairment: The pharmacokinetics of lamotrigine in patients with impaired liver function have not been evaluated.

repaired impairments of provide the evaluated. Gilbert's Syndrome: Gilbert's syndrome (idiopathic unconjugated hyperbilinubinemia) does not appear to affect the

pharmacokinetic profile of lamotrigine. Concomitant Antiepileptic Drugs: In patients with epilepsy, concomitant administration of LAMICTAL with enzyme-Concommant Antiepheput Drugs: In patents with epilepsy, concommant administration of Drugor TAL with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone or phenobarbital) decreases the mean lamotrigine t<sub>1/2</sub> to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases t<sub>1/2</sub> and decreases the dearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong t<sub>1/2</sub> up to approximately 27 hours. Acetaminophen was shown to slightly decrease the t<sub>1/2</sub> and increase the dearance of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1.

#### Table1 : Mean Pharmacokinetic Parameters in Adult Patients with Epilepsy or Healthy Volunteers

		Healthy Young Volunteers		Pati	ents with Epile	ipsy
	LAMICTAL Administered	LAMICTAL	LAMICTAL+ Valproic Acid <sup>2</sup>	LAMICTAL +Enzyme- Inducing AEDs	LAMICTAL+ Vatproic Acid	LAMICTAL+ Valproic Acid +Enzyme- Inducing AEDs
Tmax	Single Dose	2.2 (0.25-12.0) <sup>1</sup>	1.8 (1.0–4.0)	2.3 (0.5–5.0)	4.8 (1.8–8.4)	3.8 (1.0–10.0)
(hrs)	Muttiple Dose	1.7 (0.5–4.0)	1.9 (0.5–3.5)	2.0 (0.755.93)	ND	ND
11/2	Single Dose	32.8 (14.0-103.0)	48.3 (31.5–88.6)	14.4 (6.4–30.4)	58.8 (30.5–88.8)	27.2 (11.2–51.6)
	Multiple Dose	25.4 (11.6–61.6)	70.3 (41. <del>9–</del> 113.5)	12.6 (7.5–23.1)	ND	ND
Plasma Clearance	Single Dose	0.44 (0.12–1.10)	0.30 (0.14–0.42)	1.10 (0.51–2.22)	0.28 (0.16–0.40)	0.53 (0.27-1.04)
(meanwaky)	Muttiple Dose	0.58 (0.24–1.15)	0.18 (0.12–0.33)	1.21 (0.66–1.82)	ND	ND

ND=Not done

Range of individual values across studies
 Valproic Acid administered chronically (Multiple Dose Study) or for 2 days (Single Dose Study)

INDICATIONS AND CLINICAL USE

LAMICTAL (lamotrigine) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy. There is limited information on the use of LAMICTAL in monotherapy

#### CONTRAINDICATIONS

CHAINCTAL (canotigine) is contraindicated in patients with known hypersensitivity to lamotrigine or to any components of the formulation. WARNINGS

WARNINGS Serious dermatologic events have been reported infrequently in patients receiving LAMICTAL (lamotrigine). Such events were more likely to occur during the first six weeks of therapy. More rapid initial litration dosing and use of oc-comitant valproic add were associated with a higher incidence of serious dermatologic events (see PRECAUTIONS, Skin-Related Events, Tables 2 and 3; see also DOSAGE AND ADMINISTRATION). These events have included Stevens-Johnson synctrome, toxic epidermal necrolysis, angioedema, and hypersensitivity syndrome (which usually consisted of fever, rash, facial swelling and other systemic involvement, e.g. hematologic, hepatic, and/or lymphatic). Hepatic injury, as part of a hypersensitivity syndrome, may have been the rititating event in one reported death. It is recommended that the physician closely monitor (including hepatic, renal and dotting parameters) patients who acutely develop any combination of unexplained rash, fever, fluidle symptoms or worsening of seizure control, especially within the first month of starting treatment. Patients who develop a rash should be promptly evaluated. LAMICTAL should be discontinued in all patients with a medically serious rash. Although many patients who developed as indicat triaks continued to receive LAMICTAL without consequences, the initial presentation of a rash is not always indicative of its eventual seriousness. The potential medical benefits of continued theragy with LAMICTAL must be weighed against the increased risk of serious rash in patients who have already developed a rash. PRECAUTIONS Drug Discontinuation

#### **Drug Discontinuation**

Abrupt discontinuation of any antiepileptic drug (AED) in a responsive patient with epilepsy may provoke rebound

seizures. In general, withdrawal of an AED should be gradual to minimize this risk. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL (amotrigine) should be tapered over a period of at least two weeks (see DOSAGE AND ADMINISTRATION). **Occupational Hazards** 

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials common adverse effects included dizziness, ataxia, drowsiness, diplopia, and blurred vision. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that LAMICTAL. does not affect them adversely. Skin-Related Events

Skin-Related Events In controlled studies of adjunctive lamotrigine therapy, the incidence of rash (usually maculopapular and/or erythematous) in patients receiving LAMICTAL was 10% compared with 5% in placebo patients. The rash usually occurred within the first six weeks of therapy and resolved during continued administration of LAMICTAL. LAMICTAL was discontinued because of rash in 1.1% of patients in controlled studies and 3.8% of all patients in all studies. The rate of rash-related withdrawal in clinical studies was higher with more rapid initial titration dosing, and in patients receiving concomitant valproice aid (VPA), particularly in the absence of enzyme-inducing ABDs. See Tables 2 and 3; see also WARNINGS, and DOSAGE AND ADMINISTRATION.

#### Table 2 : Effect of Concomitant AEDs on Rash Associated with LAMICTAL in All Controlled and Uncontrolled **Clinical Trials Regardless of Dosing Escalation Scheme**

AED Group	Total Patient Number	All Rashes	Withdrawal Due to Rash	Hospitalization In Association with Rash
Enzyme-Inducing AEDs <sup>1</sup>	1788	9.2%	1.8%	0.1%
Enzyme-Inducing AEDs <sup>1</sup> + VPA	318	8.8%	3.5%	0.9%
VPA <sub>st</sub> Non-Enzyme-Inducing AEDs <sup>2</sup>	159	20.8%	11.9%	2.5%
Non-Enzyme-Inducing AEDs <sup>2</sup>	27	18.5%	0.0%	0.0%

1 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone 2 Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin

Table 3 : Effect of the Initial Daily Dose1 of LAMICTAL in the Presence of Concomitant AEDs, on the Incidence of Rash Leading to Withdrawal of Treatment in Add-On Clinical Triats

AED Group	Enzyme-In	ducing AEDs <sup>2</sup>	Enzyme AEDs	Hnducing <sup>2</sup> + VPA	VPA ± No Inducir	on-Enzyme- ng AEDs <sup>3</sup>
LAMICTAL	Total	Percentage of	Total	Percentage of	Total	Percentage of
Average	Patient	Patients	Patient	Patients	Patient	Patients
Daily Dose (mg)	Number	Withdrawn	Number	Withdrawn	Number	Withdrawn
12.5	9	0.0	10	0.0	51	7.8
25	3	0.0	7	0.0	58	12.1
50	182	1.1	111	0.9	35	5.7
100	993		179	4.5	15	40.0
>195	601	1 28	11	1 182 1	1 0	1 00

1 Average daily dose in week 1 2 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone 3 Non-enzyme-inducing AEDs include donazepam, clobazam, ethoswimide, methswimide, vigabatrin, and

gabapentin

Increased incidence of rash-related withdrawal was seen when initial doses were higher and titration more rapid than recommended under DOSAGE AND ADMINISTRATION. Drug Interactions

urug interactions Antiepileptic Drugs (AEDs): Lamotrigine does not affect the plasma concentrations of concomitantly administered enzyme-inducing AEDs. Antiepileptic drugs that induce hepatic drug-metabolizing enzymes (phenytoin, carba-mazepine, phenobarbital, primidone) increase the plasma clearance and reduce the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY).

(see ACTION AND CLINICAL PHAMMCOLOGY). Valproic acid reduces the plasma clearance and protongs the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY). When LAMICTAL was administered to 18 healthy volunteers already receiving valproic acid, a modest decrease (25% on average) in the trough steady-state valproic acid plasma concentrations was observed over a 3-week period, followed by stabilization. However, the addition of LAMICTAL did not affect the plasma concentration of valproic acid in patients receiving enzyme-inducing AEDs in combination with valproic acid. See also PRECAUTIONS, Skin-Related Events.

Oral Contraceptives: In a study of 12 female volunteers, LAMICTAL did not affect plasma concentrations of ethiny-loestraciol and levonorgestrel following administration of the oral contraceptive pill. However, as with the introduction of other chronic therapy in patients taking oral contraceptives, the patient should be asked to report any change in the manufactual begins on them.

mensional being pattern. Drugs Depressing Cardiac Conduction: (see Patients with Special Diseases and Conditions). DrugsLaboratory Test Interactions: LAMICTAL has not been associated with any assay interferences in clinical laboratory tests

Taboratory tests. Use in the Elderhy The safety and efficacy of LAMICTAL in elderhy patients with epilepsy have not been systematically evaluated in clinical trials. Caution should thus be exercised in does election for an elderhy patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions and limited experience with LAMICTAL in this population. Use in Children The safety and efficacy of LAMICTAL in children under 18 years of age have not yet been established.

Use in Obstetrics

The sately and encacy of Device 1AL in Calification Index in Syears of age have not yet been established. Use in Obstetrics Pregnancy: Studies in mice, rats and rabbits given lamotrigine orally or intravenously revealed no evidence of treatogenicity; however, maternal and secondary fetal toxicity were observed. Studies in rats and rabbits indicate that lamotrigine crosses the placenta; placental and fetal levels of lamotrigine were low and comparable to levels in maternal plasma. Because animal reproduction studies are not always predictive of human response, LAMICTAL, should only be used during pregnancy if the benefits of therapy outweigh the risks associated with it. Clinical trials data indicate that lamotrigine has no effect on blood fotate concentrations in adults; however, its effects during human fetal development are unknown. Labor and Delivery: The effect of LAMICTAL in labor and delivery in humans is unknown. Nursing Mothers: LAMICTAL is excreted in human milk. Because of the potential for adverse reactions from LAMICTAL in nursing infants, breast-leveding while taking this medication is not recommended. Patients with Special Diseases and Conditions Clinical experience with LAMICTAL in patients with concomitant illness is limited. Caution is advised when using LAMICTAL in patients with diseases or conditions that could affect the metabolism or elimination of the drug. Patients with PARMACOLOGY). Use of LAMICTAL in patients with borned renal function (see ACTION AND CLINICAL PHARMACOLOGY). Use of LAMICTAL in patients with bus of LAMICTAL in patients of the protent and individuals with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY). Use of LAMICTAL in patients with severe renal impairment should proceed with aution.

CLINICAL PHARIMACOLOGY). Use of LAMICTAL in patients with severe renal impairment should proceed with caution. Impaired Liver Function: There is no experience with the use of LAMICTAL in patients with impaired liver function. Caution should be exercised in dose selection for patients with this condition. Cardiac Conduction Abnormalities: One placebo-controlled trial that compared electrocardiograms at baseline and during treatment, demonstrated a mild prolongation of the P-R interval associated with LAMICTAL administration. The prolongation was statistically significant but clinically insignificant. Patients with significant cardiovascular disease or electrocardiographic abnormalities were, however, systematically excluded from clinical trials. Thus, LAMICTAL should be used with caution in patients with cardiac conduction abnormalities, and in patients taking concomitant medications which depress AV conducton. Dependence Liability

Dependence Lability No evidence of abuse potential has been associated with LAMICTAL, nor is there evidence of psychological or physical dependence in humans. Laboratory Tests The use of LAMICTAL does not require routine monitoring of any dinical laboratory parameters or plasma levels of concornitant AEDs. ADVERSE REACTIONS

ADVERSE REACTIONS Adverse experiences in patients receiving LAMICTAL (lamotigine) were generally mild, occurred within the first two weeks of therapy, and resolved without discontinuation of the drug. Commonly Observed The most commonly observed adverse experiences associated with the use of adjunctive therapy with LAMICTAL (incidence of at least 10%) were dizziness, headache, diplopia, somnolence, ataxia, nausea, and asthenia.

Dizziness, diplopia, ataxia, and blurred vision were dose-related and occurred more commonly in patients receiving carbamazepine in combination with LAMICTAL than in patients receiving other enzyme-inducing AEDs with LAMICTAL. Reduction of the daity dose and/or alteration of the timing of doses of concomitant antiepileptic drugs and/or LAMICTAL may reduce or eliminate these symptoms. Clinical data suggest a higher incidence of rash in patients who are receiving concomitant valproic acid, or non-inducing AEDs (see WARNINGS; see also PRECALTONS, Skin-Related Events, Table 2). Associated with Discontinuation of Treatment

Associated with Discontinuation of Treatment in controlled clinical intals, 6.9% of the 711 patients receiving LAMICTAL discontinued therapy due to an adverse expe-rience, versus 2.9% of the 419 patients receiving placebo. Of 3501 patients and volunteers who received LAMICTAL in premarketing clinical studies, 358 (10.2%) discontinued therapy due to an adverse experience. Across all studies, the most common adverse experiences associated with discontinuation of LAMICTAL were rash, dizziness, headabhe, ataxia, nausea, diplopia, somnolence, seizure exacertation, astheria, and blurred vision. Discontinuation due to an adverse experience classified as serious occurred in 2.3% of patients and volunteers who received LAMICTAL in the premarketing studies. Rash accounted for almost hard of the discontinuations due to serious adverse experiences. More rapid initial titration dosing of LAMICTAL, and concomitant use of valproic acid were associated with higher incidences of rash-related withdrawal in clinical studies (see WARNINGS; see also PRECAUTIONS, Skin-Related Events, Table 3). Controlled Clinical Studies

Controlled Clinical studies Table 4 numerates adverse experiences that occurred with an incidence of 2% or greater among refractory patients with epilepsy treated with LAMICTAL. Other Events Observed During Clinical Studies: During clinical testing, multiple doses of LAMICTAL were administered to 3501 patients and volunteers. The conditions and duration of exposure to LAMICTAL during these clin-ical studies varied greatly. Studies included monotherapy and pediatric trials. A substantial proportion of the exposure was gained in open, uncontrolled clinical studies. Adverse experiences associated with exposure to LAMICTAL were space to the studies of the studies clinical studies. was gailed in open, into into a studies. Are as a studies and into a studies are studied and the studies of the studies are studied and the studies of the studies are studied and the properties of individuals experiencing adverse events without first grouping similar types of adverse experiences into a smaller number of standardized event categories.

acverse experiences into a smaller number of standardized event categories. Since the adverse experiences reported occurred during treatment with LAMICTAL in combination with other antipplieptic drugs, they were not necessarily caused by LAMICTAL. The following adverse events have been reported on one or more occasions by at least 1% of patients and volunteers exposed to LAMICTAL: anorexia, weight gain, amnesia, concentration disturbance, confusion, emotional lability, nervousness, nystagmus, paresthesia, thinking abnormality and vertigo. (All types of events are included except those already listed in Table 4.)

Table 4 Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Studies<sup>1</sup>

Body System/	Percent of Patients Receiving LAMICTAL (and other AEDs)	Percent of Patients Receiving Placebo (and other AEDs)	Percent of Patients Receiving LAMICTAL (and other AEDs) Who Were Discontinued
Adverse Experience <sup>2</sup>	(n=711)	(n=419)	(n=711)
BODY AS A WHOLE			
Headache	29.1	19 1	13
Accidental Injury	91	86	01
Asthenia	86	8.8	0.3
Flu Syndrome	7.0	5.5	0.0
Pain	62	20	0.1
Pack Pain	5.0	2.0	0.1
Eovor	5.5	0.2	0.0
Abdeminel Dain	5.5	3.0	0.1
Abgominal Fam	5.2	3.0	0.1
Neek Dein	9.4	4.1	0.0
Neck Pain	2.4	1.2	0.0
Malaise	2.3	1.9	0.3
Seizure Exacerdati	on 2.3	0.5	0.3
DIGESTIVE	40.0		4.0
Nausea	18.6	9.5	1.3
Vomiting	9.4	4.3	0.3
Diarrhea	6.3	4.1	0.3
Dyspepsia	5.3	2.1	0.1
Constipation	4.1	3.1	0.0
Tooth Disorder	3.2	1.7	0.0
MUSCULOSKELETAL			
Myalgia	2.8	3.1	0.0
Arthraigia	2.0	0.2	0.0
NERVOUS			
Dizziness	38.4	13.4	2.4
Ataxia	21.7	5.5	0.6
Somnolence	14.2	6.9	0.0
Incoordination	6.0	2.1	0.3
Insomnia	56	19	0.4
Tremor	4.4	1.4	0.0
Depression	4.2	26	0.0
Anviety	3.8	26	0.0
Convulsion	3.0	1.0	0.0
Irritability	3.2	1.2	0.3
Speech Disorder	3.0	1.9	0.1
Speech Disoluel	2.0	0.2	0.1
	1 2.4	1.9	0.0
Deinitio	10.0		0.0
Bhannas	13.0	9.3	0.0
Pharyngius	9.8	8.8	0.0
Cougn Increased	7.5	5.7	0.0
Hespiratory Disordi	Br 5.3	5.5	0.1
SKIN AND APPENDAGI	=5		
Hash	10.0	5.0	1.1
Pruntus	3,1	1.7	0.3
SPECIAL SENSES		~ -	<b>A</b> =
Diplopla	27.6	6.7	0.7
Blurred Vision	15.5	4.5	1.1
Vision Abnormality	3.4	1.0	0.0
UROGENITAL			
Female Patients	(n=365)	(n=207)	
Dysmenorrhea	6.6	6.3	0.0
Menstrual Disorder	5.2	5.8	0.0
Vaginitis	4.1	0.5	0.0

Patients in these studies were receiving 1 to 3 concomitant enzyme-inducing antiepileptic drugs in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation. Thus, patients may be included in more than one category.
 Adverse Experiences reported by al least 2% of patients treated with LAMICTAL are included.

Other Events Observed During Clinical Practice and from "Compassionate Plea" Patients: In addition to the adverse experiences reported during dinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving LAMICTAL marketed in other countries and from worldwide 'compassionate plea' patients. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: Apnea, erythema multilorme, esophagitis, hematemess, hemotycic amenia, pancreatitis, pancytopenia and progressive immunosuppression. SYMPTOMS AND TREATMENT OF OVERDOSAGE

During the clinical development program, the highest known overdose of LAMICTAL (lamotrigine) occurred in a 33-year

old female who ingested between 4000 and 5000 mg LAMICTAL that corresponded to a plasma level of 52µg/mL four hours after the ingestion. The patient presented to the emergency room comatose and remained comatose for 8 to 12 hours, returned to almost normal over the next 24 hours, and completely recovered by the third day. There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including irequent moritoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In six renal failure patients, about 20% of the amount of lamotrigine in the body was removed during 4 hours of hemodialysis. **DOSAGE AND ADMINISTRATION** 

#### Adults

Adults
LAMICTAL (lamotrigine) is intended for oral administration and may be taken with or without food. LAMICTAL should
be added to the patient's current antiepileptic therapy.
Hepatic enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, and primidone reduce the eliminattion half-life of lamotrigine and reduces the plasma dearance by DS% (see ACTION AND CLINICAL PHARIMA
COLOGY). These dinically important interactions require dosage schedules of LAMICTAL as build be added to the patient's ourent interactions require dosage schedules of LAMICTAL as the elimination tail-file of lamotrigine and reduces the plasma dearance by DS% (see ACTION AND CLINICAL PHARIMA
COLOGY). These dinically important interactions require dosage schedules of LAMICTAL as a summarized in Table 5.
LAMICTAL does not alter plasma concentrations of concomitantly administered enzyme-inducing AEDs and therefore
they do not usually require dose adjustment to maintain therapeutic plasma concentrations. For patients receiving
LAMICTAL in combination with other AEDs, an evaluation of all AEDs in the regimen should be considered if a charge
in seizure control or an appearance or worsening of adverse experiences is observed. If there is a need to discontinue
therapy with LAMICTAL, a step-wise reduction of dose over at least two weeks (approximately 50% per week) is
recommended unless safety concerns require a more rapid withdrawal (see PRECAUTIONS).
The relationship of plasma concentration to clinical response has not been established for lamotrigine. Dosing of
LAMICTAL should be based on therapeutic response has not been established for lamotrigine. Dosing of
LAMICTAL should be based on therapeutic response has not been established for lamotrigine. Dosing of
LAMICTAL should be based on therapeutic response has not been established for lamotrigine. Dosing of
LAMICTAL should be based on therapeutic response. In controlled clinical studies, doses of LAMICTAL that were
efficacious generality protoded steady-state trough plasma lamotr

For Information\*

Table 5 LAMICTAL Recommended Dosage Schedule for Adults

	Patient		
Treatment Week	Enzyme-Inducing AEDs <sup>1</sup> Without Valproic Acid	Enzyme-Inducing AEDs <sup>1</sup> With Valproic Acid	Patients Taking Valproic Acid Only
Weeks 1+2	50 mg once a day	25 mg once a day	25 mg every other da
Weeks 3 + 4	50 mg twice a day	25 mg twice a day	25 mg once a day
Usual Maintenance	150-250 mg twice a day	50-100 mg twice a day	50-100 mg twice a da
			* Column milloote doose

1 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

ng every other day ng once a day 00 mg twice a day umn reflects dosage recommendations in the United Kingdom and is provided for information.

Optimal escalation doses from Week 5 to maintenance have not been fully established; titration is subject to Clinical evaluation of the patient. There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on LAMICTAL.

There have been to controlled studies to establish the electroness of optimal dosing regime of laboral DWICTAL therapy in patients receiving only non-enzyme-inducing AEDs or valproic add. However, available data from open clinical trials indicate that the addition of LAMICTAL under these conditions is associated with a higher incidence of serious rash or rash-related withdrawal, even at an iritial itration dose of 12.5 mg daily (see PRECAUTIONS, Skin Related Events, Table 3; see also WARINIGS). The potential medical benefits of addition of LAMICTAL under these conditions must be weighed against the increased risk of serious rash. If use of LAMICTAL under these conditions is considered dinically indicated, itration dosing should proceed with extreme caution, especially during the first six weeks of dose itration. of dose titration.

of dose titration. Withdrawal of Concomitant AEDs: In patients receiving LAMICTAL who have all concomitant enzyme-inducing AEDs withdrawn, the t<sub>1/2</sub> of tamotrigine will be approximately doubled (see ACTION AND CLINICAL PHARMACOLO GY). Under these conditions, it may be necessary to reduce the dose of LAMICTAL. In contrast, in patients receiving LAMICTAL who have valproic add withdrawn, the t<sub>1/2</sub> of tamotrigine will be decreased; under these conditions, it may be necessary to increase the dose of LAMICTAL. In editation should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions. Patients with Impaired Renal Function: The elimination half-life of tamotrigine is prolonged in patients with impaired renal function (see ACTION AND CLINICAL PHARMACOLOGY). Caution should be exercised in dose selection for patients with Impaired Renal Function:

Terms uncarent (see Arch Trurk AND CULINICAL PHAHMACULOGY). Caution should be exercised in dose selection for patients with impaired renal function. Patients with impaired Hepatic Function: There is no experience with the use of LAMICTAL in patients with impaired liver function. Because lamotrigine is metabolized by the liver, caution should be exercised in dose selection for patients with this condition. Call the selection of the liver of

Dosage recommendations for children under 18 years of age are not yet established. PHARMACEUTICAL INFORMATION

Chemical Name:

Trug Substance Brand Name: LAMICTAL Common Name: Lamotigine Chemical Name: 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-

[USAN]

6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine



[Chern, Abstr.] Structural Formula:

#### Composition

Composition
LAMICTAL Tablets contain lamotrigine and the following non-medicinal ingredients:
- callulose, lactose, magnesium stearate, povidone, sodium starch glycolate and coloring agents:
- 25 mg (white tablets)
- None
- 100 mg (peach tablets)
- Sunset Yellow FCF Lake
- 150 mg (cream tablets)
- Ferric Oxide, Yellow
Stability and Storage Recommendations
LAMICTAL Tablets should be stored at controlled nom temperature (15°C to 30°C) in a dry place and protected from light.
AVAILABILITY OF DOSAGE FORMS
LAMICTAL Tablets on policy different dimensional temperature (15°C to 30°C) in a dry place and protected from light.

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Product Monograph available upon request.

Product Monograph available upon request. References: 1. Goa KL *et al.* Lamotrigine: A review of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 1993;46(1):152-176. 2. Brotel MJ. Lamotrigine versus other antiepilepitc drugs: A star rating system is born. *Epilepsis* 1994;35(Sup. 5):451-546. 3. LAMICITAL Product Monograph. 4. Richers A, Yuen AWC. Overview of the din-ical efficacy of lamotrigine. *Epilepsis* 1991;32(Sup. 2):S13-S16. 5. Betts T *et al.* Human safety of lamotrigine. *Epilepsis* 1991;32(Sup.2):S17-S21. 6. Brinnic ED. The efficacy of lamotrigine. *Rev Contemp Pharmacother* 1994;5:115-122. 7. Yuen AWC. Lamotrigine (Lamictal) for refractory partial epilepsis 1993;42(3):153-536. 8. Jawad S *et al.* Controlled trial of lamotrigine (Lamictal) for refractory partial epilepsy. *Epilepsis* 1993;32(Sup.2):353-536. 8. Jawad S *et al.* Controlled trial of lamotrigine (Lamictal) for refractory partial epilepsy. *Epilepsis* 1993;32(Sup.2):353-536. 8. Jawad S *et al.* Controlled trial of lamotrigine (Lamictal) for refractory partial epilepsy. *Epilepsis* 1993;32(2):312-322. 10. Loiseau P *et al.* A randomised double-blind placebo-controlled crossover add-on trial of almotrigine in patients with transment-resistant partial seizures. *Epilepsy Res* 1990;7(2):136-145. 11. Matsuo F *et al.* Pacebo-controlled trial (BW300C), rapiteria, a poten-tial anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. *B. J. Clin Pharmac* 1985;20:619-629. 13. Leach MJ *et al.* Neurochemical and behavioral aspects of lamotrigine. *Epilepsis* 1991;32(Suppl. 2):54-58.



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#### ACTION AND CLINICAL PHARMACOLOGY

SABRIL (vigabatrin) is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain. The mechanism of action of vigabatrin is attributed to irreversible enzyme inhibition of GABA-T, and consequent increased levels of the inhibitory neurotransmitter, GABA.

Decreased serum levels of SGOT (ALT) and SGPT (AST) have been observed during treatment with vigabatrin and may be the result of inhibition of these transaminases by vigabatrin. The clinical significance of these findings is unknown.

The duration of effect of vigabatrin is thought to be dependent on the rate of GABA-T resynthesis rather than on the plasma concentration of vigabatrin.

#### **Clinical Trials**

In clinical trials, including double-blind, placebo-controlled studies involving 354 patients with drug-resistant complex partial seizures, vigabatrin reduced seizure frequency by 50% or more in approximately half of the patients studied.

In clinical trials involving children, the efficacy of vigabatrin was similar to that seen in adult patients with retractory partial seizures. In one study of 70 children with intractable infantile spasms, approximately 70% of the patients had a greater than 50% reduction in spasms. In this study, long-term response was observed in 75% of the children with symptomatic infantile spasms and 36% of the children with cryptogenic infantile spasms.

#### **Pharmacokinetics**

Vigabatrin is rapidly absorbed following oral administration and peak plasma concentrations are reached within two hours. Vigabatrin is widely distributed with an apparent volume of distribution slightly greater than total body water. The primary route of elimination is via the kidney, with little metabolic transformation occurring. Following a single dose, approximately 70% is excreted in the urine as unchanged drug within the first 24 hours post-dose. The plasma elimination half-life is approximately 5-8 hours in young adults and 12-13 hours in the elderly. In renal impairment the elimination is prolonged and the rate of renal clearance is directly relaed to creatinine clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Vigabatrin does not induce the hepatic cytochrome P450 system nor is it extensively metabolized or plasma-protein bound. Administration of vigabatrin with food slightly reduces the rate, but not the extent of absorption.

#### INDICATIONS AND CLINICAL USE

SABRIL (vigabatrin) is indicated for the adjunctive management of epilepsy which is not satisfactorily controlled by conventional therapy. There is insufficient data on the usefulness of vigabatrin in monotherapy at this time.

Vigabatrin should be used under close monitoring by a neurologist. CONTRAINDICATIONS

SABRIL (vigabatrin) is contraindicated in pregnancy and lactation (see WARNINGS) and in patients with a known hypersensitivity to vigabatrin or to any components of the product.

# WARNINGS

#### **Neurotoxicity in Animals**

Rat, Mouse and Dog: Safety studies carried out in the rat, mouse and dog at doses of 30 to 50 mg/kg/day and higher, caused doseand time-dependent micro-vacuolation within certain white matter tracts of the brain (the cerebellum, reticular formation and thalamus in rodents and the columns of the fornix and optic tracts in dogs were most affected). The microvacuolation was caused by the separation of the outer lamellar sheath of myelinated fibres, a change characteristic of non-inflammatory intramyelinic edema.

In both the rat and dog (mouse was not tested), the intramyelinic edema was reversible after stopping the administration of vigabatrin; however, in the mouse and rat, residual changes consisting of swollen axons and mineralised microbodies were observed.

Monkey: In monkeys, the oral administration of 300 mg/kg/day for 16 months produced minimal microvacuolation with equivocal differences between treated and control animals. Low oral absorption of vigabatrin in the monkey resulted in an actual absorbed dose of 75 mg/kg/day. In spite of the poor absorption, cerebrospinal fluid (CSF) levels of vigabatrin in the monkeys were comparable to those seen in rats treated with 300 mg/kg/day; however, GABA levels in the CSF and the brain cortex in treated monkeys were not significantly different from untreated monkeys. This finding may explain the reason for the equivocal effects, since the intramyelinic edema associated with vigabatrin treatment appears to be related to increased brain GABA levels.

#### **Evoked Potentials**

Evoked potentials in animals: In the dog, studies indicate that intramyelinic edema is associated with increased latencies in somatosensory and visual evoked potentials. Magnetic resonance imaging (MRI) changes also correlated with intramyelinic edema in the fornix, thalamus and hypothalamus.

Evoked potentials in man: No increased evoked potential latencies have been observed in man. Two hundred and twenty-one patients treated for 4-5 months showed no significant evoked potential latency changes at the end of treatment as compared to baseline. MRI results in man did not show the changes observed in dogs who had intramyelinic edema.

Postmortem neuropathological changes seen in 11 patients who were treated with vigabatrin (mean duration of treatment was 28 months, and the longest treatment was 6 years) showed no myelin vacuolation in the white matter that was considered to be outside of the control range.

Although clinical trials have not revealed the type of neurotoxicity seen in animal studies, because of increased CSF GABA levels observed in humans, it is recommended that patients treated with vigabatrin be closely observed for adverse effects on neurological function, with special attention to visual disturbance.

Use in Pregnancy and Lactation In a teratology study in the rabbit a dose-related incidence, 2% and 9%, of cleft palate was observed at doses of 150 and 200 mg/kg/day, respectively.

In animal reproductive studies neurohistopathology was not performed on the fetuses, therefore it is not known whether microvacuotation occurred in utero. The possibility that microvacuotation or other neurotoxicity may occur in human fetuses cannot be discarded.

### PRECAUTIONS

Use in Patients with a History of Psychosis Behavioural disturbances such as aggression and psychotic episodes have been reported following initiation of vigabatrin therapy. A history of abnormal behaviour or psychosis appears to be a predisposing factor for such reactions, therefore treatment in such patients should be initiated cautiously at low doses and with frequent monitoring.

Use in the Elderly and in Patients with Renal Impairment Vigabatrin is eliminated via the kidney and caution should be exercised when administering the drug to elderly patients and to patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Use in Patients with Myoclonic Seizures As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with vigabatrin. Patients with myoclonic seizures may be particularly liable to this effect.

Discontinuation of Therapy As with other antiepileptic drugs, abrupt discontinuation may lead to rebound seizures. If a patient is to be withdrawn from vigabatrin treatment, it is recommended that this be done gradually by reducing the dose over a 2 to 4 week period if possible. Drug Interactions A gradual reduction of about 20% in plasma phenytoin concentration has been observed following add-on therapy with vigabatrin. The mechanism whereby this occurs is unknown. Limited data from clinical trials suggest that increasing the phenytoin dose to compensate may not be necessary.

Occupational Hazards Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were drowsiness and fatigue. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that vigabatrin does not affect them adversely.

#### ADVERSE REACTIONS

SABRIL (vigabatrin) is generally well tolerated in epileptic patients. Adverse events are mainly CNS-related and probably a secondary consequence of increased GABA levels caused by vigabatrin. The safety of vigabatrin was evaluated in 2081 epileptic patients treated in clinical trials. The relationship of adverse events to vigabatrin therapy was not clearly established as patients were taking other antiepileptic drugs concomitantly. The most frequently reported adverse events were somnolence (12.5%), fatigue (9.2%), and weight gain (5.0%). The following adverse events were observed in more than 1% of patients:

Adverse Events Reported By More Than 1% of Patients				
Body System/ Adverse Event	Number of Patients	Incidence n=2081		
Nervous				
somnolence headache dizziness nervousness depression memory disturbances diplopia aggression ataxia vertigo hyperactivity vision abnormal confusion insomnia impaired concentration	261 80 79 56 52 47 46 39 39 37 34 29 26 25	12.5 3.8 3.8 2.7 2.5 2.3 2.2 2.0 1.9 1.9 1.8 1.6 1.4 1.3 1.2		
personality disorder agitation	23 23 21	1.1 1.0		
Digestive				
abdominal pain constipation vomiting nausea	34 29 28 28	1.6 1.4 1.4 1.4		
Body as a Whole				
fatigue weight gain asthenia	192 104 23	9.2 5.0 1.1		

Adverse events reported with a frequency of less than 1% include: anxlety, emotional lability, behavioural disturbances including psychosis, irritability, tremor, abnormal gait, speech disorder, increased appetite, and dyspepsia.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with vigabatrin treatment (see PRECAUTIONS).

Laboratory data indicate that vigabatrin treatment does not lead to renal or hepatic toxicity. Chronic treatment with vigabatrin may be associated with a slight decrease in hemoglobin, which rarely attains clinical significance.

Pediatric Safety Safety data is available in 299 children, aged 2 months to 16 years (1 patient was 18 years of age), participating in clinical trials with vigabatrin. Relationship of adverse events to vigabatrin therapy was not clearly established as children were taking other antiepileptic drugs concomitantly.

The most frequent adverse event observed in children was "hyperactivity" (reported as hyperkinesia 7.7%, agitation 2.3%, excitation 0.3% or restlessness 0.7%), which was observed in 11.0% of children, an incidence higher than that seen in adults. Other commonly reported adverse events were somnolence (8.0%) and weight gain (3.0%).

The following adverse events were reported in children with a frequency greater than 1%:

Adverse Events Reported By More Than 1% of Pediatric Patients		
Body System/ Adverse Event	Number of Patients	Incidence n=299
Nervous		
somnolence hyperkinesia aggression insomnia aggitation ataxia emotional lability headache increased seizures	24 23 8 7 7 3 3 3 3	8.0 7.7 2.7 2.3 2.3 1.0 1.0 1.0
Digestive vomiting nausea increased saliva	6 3 3	2.0 1.0 1.0
<b>Body as a Whole</b> weight gain fatigue hypotonia	9 8 3	3.0 2.7 1.0

#### SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific antidote. The usual supportive measures should be employed.

Two cases of SABRIL (vigabatrin) overdose have been reported. In the first case, the patient accidentally took a dose of 14 g daily for 3 days and transient vertigo and tremor were reported. In the second case, an 18-year old female took 30 g of vigabatrin and 250 mg of chlorazepate in a suicide attempt. The patient was admitted to hospital in a state of coma which lasted four days; however, the coma was considered to be due to the chlorazepate rather than vigabatrin. The patient recovered without sequelae.

#### DOSAGE AND ADMINISTRATION

SABRIL (vigabatrin) is intended for oral administration once or twice daily and may be taken with or without food. Sabril should be added to the patient's current antiepileptic therapy. Instructions to the patient on the use of SABRIL are provided in the

INFORMATION FOR THE CONSUMER section.

Adults The recommended starting dose is 1 g/day, although patients with severe seizure manifestations may require a starting dose of up to 2 g/day. The daily dose may be increased or decreased in increments of 0.5 g depending on clinical response and tolerability. The optimal dose range is between  $2 \cdot 4$  g/day, Increasing the dose beyond 4 g/day does not usually result in improved efficacy and may increase the occurrence of adverse reactions.

**Children** The recommended starting dose in children is 40 mg/kg/day, increasing to 80 - 100 mg/kg/day depending on response. Therapy may be started at 0.5 g/day, and raised by increments of 0.5 g/day weekly depending on clinical response and tolerability.

Bodyweight	Daily Dose	No. Tablets/Day
10 - 15 kg	0.5 – 1 g/day	1 – 2 tablets/day
16 - 30 kg	1 – 1.5 g/day	2 – 3 tablets/day
31 - 50 kg	1.5 – 3 g/day	3 – 6 tablets/day
> 50 kg	2 – 4 g/day	4 – 8 tablets/day

Elderly and Renally Impaired Patients Vigabatrin is almost exclusively eliminated via the kidney and, therefore, caution should be exercised when administering the drug to the elderly, and more particularly to patients with creatinine clearance less than 60 mL/min. It is recommended that such patients be started on a lower dose of vigabatrin and observed closely for adverse events such as sedation and confusion.

#### AVAILABILITY OF DOSAGE FORMS

Tablets Each SABRIL (vigabatrin) 500 mg tablet is white to offwhite film-coated, oval biconvex, and imprinted "SABRIL" on one side. SABRIL is available in HDPE bottles containing 100 tablets.

Product Monograph available upon request

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See page ix.

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The Canadian Stroke Consortium is a national academic network of neurologists and neuroscience researchers, many of whom are leading contributors to cerebrovascular research in Canada.

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# WHEN THE GOAL IS TOTAL CONTROL, ADD FOR A COMPREHENSIVE APPROACH TO 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]. Potentiation 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 (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If Frisium is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant. Anterograde amnesia: Anterograde amnesia is known to occur after administration of benzodiazepines. Use in patients with depression or psychosis: Frisium is not recommended for use in patients with depressive disorders or psychosis. PRECAUTIONS Driving and Hazardous Activities: Frisium (clobazam) possesses a mild central nervous system depressant effect, therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy. Use in the Elderly: Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions Dependence Liability: Frisium should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, Frisium should be withdrawn gradually. Tolerance: Loss of part or all of the anti-convulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development. The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur. Use in Mental and Emotional Disorders: It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, Clobazam should not be used in patients suspected of having psychotic tendencies. Use in Patients with Impaired Renal or Hepatic Function: Clobazam requires dealkylation and hydroxylation before conjugation. Usual precautions should be taken if Frisium is used in patients who may have some impairment of renal or hepatic function. It is suggested that the dose in such cases be carefully titrated. In patients for whom prolonged

therapy with Frisium is indicated, blood counts and liver function should be monitored periodically. Use in Patients with Acute, Severe Respiratory Insufficiency: In patients with acute, severe respiratory insufficiency, respiratory function should be monitored. Laboratory Tests: If Frisium is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable. Drug Interactions: Most studies of the potential interactions of clobazam with other anti-epileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur. Alcohol may also significantly increase plasma clobazam levels. Several of the established anti-epileptic agents: carbamazepine, diphenylhydantoin, phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethylclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenylhydantoin. Toxicologic Studies: In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver. 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 sideeffects. 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. DOSAGE 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

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> Dr. James A. Sharpe, Professor and Chairman, Division of Neurology, University of Toronto, 399 Bathurst St., ste EC6-022, Toronto, Ontario, Canada M5T 2S8 Fax: (416) 603-5596

# NEUROSURGEONS

The Department of Surgery, Faculty of Medicine, University of Manitoba and its affiliated teaching hospitals, the Health Sciences Centre and the St. Boniface General Hospital, are seeking two contingent geographic full-time neurosurgeons at the rank of Assistant Professor. Both appointments are contingent on final budget approval. Candidates must have senior specialty qualifications in neurosurgery in the country of current practise and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification in neurosurgery by the Royal College of Physicians and Surgeons of Canada is preferred.

We are seeking qualified neurosurgeons with demonstrated expertise in the provision of exemplary advanced neurosurgical care, research and teaching. The two teaching hospitals affiliated with the University of Manitoba are the only institutions providing neurosurgical care in the Province of Manitoba. There is strong academic and clinical expertise in neurology, neuroradiology, neuropathology, neurophysiology, paediatrics and other affiliated specialties. The program incorporates a rich mix of acute and elective neurosurgical practise. The residency training program is fully accredited with the Royal College of Physicians and Surgeons of Canada and continues to attract excellent trainees. The Department of Surgery has a Masters of Science Program and PhD qualifications are provided in associated specialties.

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. Priority consideration will be given to Canadian citizens and permanent residents. Interested candidates should apply, enclosing a curriculum vitae in writing to:

Dr. R.J.W. Blanchard, Head, Department of Surgery, Health Sciences Centre GC411-820 Sherbrook St., Winnipeg, Manitoba, Canada R3A 1R9

Closing date for receipt of applications is August 31, 1995.

## **SECTION HEAD - NEUROSURGERY**

The Department of Surgery, Faculty of Medicine, University of Manitoba and its affiliated teaching hospitals, the Health Sciences Centre and the St. Boniface General Hospital, are searching for a contingent geographical full-time Head of the Section of Neurosurgery. The responsibilities include the coordination of clinical services between the two hospitals, as well as organization and supervision of undergraduate medical education and post-graduate training. The incumbent shall foster research initiatives.

The two teaching hospitals affiliated with the University of Manitoba are the only institutions providing neurosurgical care in the Province of Manitoba. There is strong academic and clinical expertise in neurology, neuroradiology, neuropathology, neuro-physiology, paediatrics and other affiliated specialties. The program incorporates a rich mix of acute and elective neurosurgical practice. The residency and training program is fully accredited with the Royal College of Physicians and Surgeons of Science Program and PhD. Qualifications are provided in associated specialities.

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 preferred.

Specific requirements include the following: substantial record of academic achievement in Neurosurgery with extensive experience in teaching and research; proven administrative experience in an academic environment; demonstrated constructive skills in interpersonal relations and communication.

Remuneration 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. Priority consideration will be given to Canadian citizens and permanent residents.

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Professor and Head, Department of Surgery, Health Sciences Centre GC411-820 Sherbrook St., Winnipeg, Manitoba, Canada R3A 1R9

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