P SINEMET® CR 200/50 100/25

(levodopa/carbidopa) CONTROLLED-RELEASE

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 levodopa/decarboxylase inhibitors or levodopa alone is limited.

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

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

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

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

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

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

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

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

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mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly.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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other adverse reactions that have been reported with levodopa or SINEMET℠ and may be potential side effects with SINEMET℠ CR are listed below:
Nervous System: Ataxia, numbness, increased hand tremor, muscle twitching, *blepharospasm, trismus, activation of latent Horner's syndrome.*
Psychiatric: Sleepiness, euphoria, paranoid ideation and psychotic episodes, and dementia.
Cardiovascular: Arrhythmias, non-specific ECG changes, flushing, phlebitis.
Gastrointestinal: Bitter taste, sialorrhea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.
Integumentary: Increased sweating, dark sweat, rash, hair loss.
Genitourinary: Urinary frequency, retention, incontinence, hematuria, dark urine, nocturia and priapism.
Special Senses: Diplopia, dilated pupils, oculogyric crises.
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℠ CR (levodopa and carbidopa) Tablets contain a 4:1 ratio of levodopa to carbidopa. SINEMET℠ CR 200/50 contains levodopa 200 mg/carbidopa 50 mg per tablet. SINEMET℠ CR 100/25 contains levodopa 100 mg/carbidopa 25 mg per tablet. The daily dosage of SINEMET℠ CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

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

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

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

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

Guideline for Initial Conversion from SINEMET℠ to SINEMET℠ CR 200/50

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

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

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

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

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

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

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

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

(384-a,4,93) 04-94-SCR-93-CDN-0040-JA

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DUPONT PHARMA

P A A B

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Epival®

(divalproex sodium)

PRESCRIBING INFORMATION

NAME OF DRUG: EPIVAL® (divalproex sodium)
Enteric-Coated Tablets

THERAPEUTIC CLASSIFICATION: Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY: EPIVAL® (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® dissociates into valproic acid in the gastrointestinal tract.
Peak serum levels of valproic acid occur in 3 to 4 hours.
The serum half-life ($t_{1/2}$) 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 glucuronidation 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 feces 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® (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® (divalproex sodium) is indicated in the treatment of the manic episodes associated with bipolar disorder (DSM-III-R).
The effectiveness of EPIVAL® in long-term use, that is for more than 3 weeks, has not been systematically evaluated in controlled trials. EPIVAL® is not indicated for use as a mood stabilizer in patients under 18 years of age.

CONTRAINDICATIONS: EPIVAL® (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® 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® (divalproex sodium).
Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed 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 acid-exposed women having children with spina bifida is approximately **1-2%**. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (ANENCEPHALY AND SPINA BIFIDA).
Animal studies have demonstrated valproic acid-induced teratogenicity (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, craniofacial 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 higher 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® (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 TOXICOLOGY: *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® (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery.
Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of EPIVAL® (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 divalproex sodium should be discontinued.
EPIVAL® (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.
There have been reports of altered thyroid function tests associated with valproic acid: the clinical significance of these is unknown.

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 circulating valproate.

Use in the Elderly: The safety and efficacy of EPIVAL® 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® in this population.

Driving and Hazardous Occupations: EPIVAL® (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.

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, if 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® (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 absence-type 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 half-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_{max} 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©. 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 valproic 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 PRECAUTIONS). 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 deficiency, bone marrow suppression and acute intermittent porphyria have been reported.

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

Metabolic: Hyperammonemia (see PRECAUTIONS), hyponatremia and inappropriate ADH secretion. Hyperglycinemia has been reported and associated with a fatal outcome in a patient with preexisting non-ketotic 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%), somnolence (19%), pain (15%), vomiting (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%), somnolence (1.9%), nausea (1.7%), and tremor (1.4%). The time to onset of these events was generally within the first two months of initial exposure to valproate. A notable exception 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 83% of patients was between 1000 mg - 2500 mg per day).

Table 1

Treatment-Emergent Adverse Event Incidence (≥ 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 $p \leq 0.05$ 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 slowing, 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© (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) equivalent to valproic acid		
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©. 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© (valproic acid) therapy, EPIVAL© should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on EPIVAL©, a dosing schedule of two or three times a day may be elected in selected patients.

PHARMACEUTICAL INFORMATION:

Drug Substance

Tradename: EPIVAL©

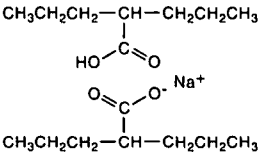
Proper Name: Divalproex sodium

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:* $C_8H_{15}NaO_4$

Structural Formula:



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, pregelatinized 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© (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© (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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Product Monograph available on request.

PAAB

See page ifc.

Intermediate Prescribing Information

℞TEGRETOL®

(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 atypical 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 SIGNS 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_1 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 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

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closely for more rapid recovery from neuromuscular blockade than expected.
Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and its active 10,11-epoxide; carbamazepine plasma levels should be monitored.
Carbamazepine, like other psycho-active drugs, may reduce 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, conjunctivitis, retinal changes, tinnitus, hyperacusis, and taste disturbances.
Endocrine system and metabolism: Occasionally edema, fluid retention, weight increase, hyponatremia and reduced plasma osmolality due to antidiuretic hormone (ADH)-like effect occurs, leading in isolated cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities. Isolated cases of gynecomastia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine i.e. FT_4, T_4,T_3, and increased TSH, usually without clinical manifestations), disturbances of bone metabolism (decrease in plasma calcium and 25-OH-calciferol), leading in isolated cases to osteomalacia, as well as reports of elevated levels of cholesterol, including HDL cholesterol and triglycerides.
Musculoskeletal system: Isolated cases - arthralgia, muscle pain or cramp.
Respiratory: Isolated cases - pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.
Hypersensitivity reactions: A rare delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, 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 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 treatment. When given in combination with lithium and 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.

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

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See pages obc, xvi.

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PARKE-DAVIS

Pr NEURONTIN*
(Gabapentin)

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 μM 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_{max} (μg/mL)	4.02	5.50
t_{max} (hr)	2.7	2.1
$t_{1/2}$ (hr)	5.2	6.1
AUC(0-∞) (μg•hr/mL)	24.8	33.3
AE%[1]	NA	63.6

[1] 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 half-life 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* does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids:

Coadministration of Neurontin with an aluminum and magnesium-based antacid reduces gabapentin bioavailability by up to 24%. Although the clinical significance of this decrease is not known, co-administration 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® 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[a] N = 543 %	Placebo[a] N = 378 %
BODY AS A WHOLE:		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
CARDIOVASCULAR:		
Vasodilatation	1.1	0.3
DIGESTIVE SYSTEM:		
Dyspepsia	2.2	0.5
Dry Mouth or Throat	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
HEMATOLOGIC AND LYMPHATIC SYSTEMS:		
Leukopenia	1.1	0.5
MUSCULOSKELETAL SYSTEM:		
Myalgia	2.0	1.9
Fracture	1.1	0.8
NERVOUS SYSTEM:		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.8
Abnormal Thinking	1.7	1.3
Twitching	1.3	0.5
Abnormal Coordination	1.1	0.3
RESPIRATORY SYSTEM:		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
SKIN AND APPENDAGES:		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
UROGENITAL SYSTEM:		
Impotence	1.5	1.1
SPECIAL SENSES:		
Diplopia	5.9	1.9
Amblyopia	4.2	1.1
LABORATORY DEVIATIONS:		
WBC Decreased	1.1	0.5

[a] 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 : hypertension

Digestive System : anorexia, flatulence, gingivitis

Hematologic and Lymphatic System : purpura; most often described as bruises resulting from physical trauma

Musculoskeletal System : arthralgia

Nervous System : vertigo, hyperkinesia, parasthesia, anxiety, hostility, decreased or absent reflexes

Respiratory System : pneumonia

Special Senses : 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 toxicity 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

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 3. Titration Schedule

DOSE	Day 1	Day 2	Day 3
900 mg/day	300 mg OD	300 mg BID	300 mg TID
1200 mg/day	400 mg OD	400 mg BID	400 mg TID

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

Total 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[a]	—	200-300[b]

[a] Loading dose of 300 to 400 mg

[b] 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.

See pages xiv, xv.

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℞BETASERON®

Interferon beta-1b

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

Description: BETASERON (Interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta$_{ser17}$. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

The specific activity of BETASERON is approximately 32 million International units (IU)/mg Interferon beta-1b. Each vial contains 0.3 mg (9.6 million IU) of Interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Dextrose and Albumin Human, USP (15 mg each/vial) are added as stabilizers. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg Interferon beta-1b.

Lyophilized BETASERON is a sterile, white to off-white powder intended for subcutaneous injection after reconstitution with the diluent supplied (Sodium Chloride, 0.54% Solution).

General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta, gamma. Interferon beta-1b, interferon alpha, and interferon gamma have overlapping yet distinct biologic activities. The activities of Interferon beta-1b are species-restricted and, therefore, the most pertinent pharmacological information on BETASERON (Interferon beta-1b) is derived from studies of human cells in culture and in humans.

Biologic Activities: Interferon beta-1b has been shown to possess both antiviral and immunomodulatory activities. The mechanisms by which BETASERON exerts its actions in multiple sclerosis (MS) are not clearly understood. However, it is known that the biologic response-modifying properties of Interferon beta-1b are mediated through its interactions with specific cell surface receptors found on the surface of human cells. The binding of Interferon beta-1b to these receptors induces the expression of a number of interferon-induced gene products (e.g., 2',5'-oligoadenylate synthetase, protein kinase, and indolamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of Interferon beta-1b. A number of these interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with Interferon beta-1b.

Clinical Trials: The effectiveness of BETASERON in relapsing-remitting MS was evaluated in a double-blind, multiclinic (11 sites: 4 Canadian and 7 United States), randomized, parallel, placebo-controlled clinical investigation of 2 years duration. MS patients, aged 18 to 50, were ambulatory (Kurtzke expanded disability status scale [EDSS] of ≤ 5.5), exhibited a relapsing-remitting clinical course, met Poser's criteria for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over 2 years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

An exacerbation was defined, per protocol, as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours.

Patients selected for study were randomized to treatment with either placebo (N=123), 0.05 mg (1.6 million IU) of BETASERON (N=125), or 0.25 mg (8 million IU) of BETASERON (N=124) self-administered subcutaneously every other day. Outcome based on the first 372 randomized patients was evaluated after 2 years.

Patients who required more than three 28-day courses of corticosteroids were removed from the study. Minor analgesics (acetaminophen), anti-depressants, and oral baclofen were allowed ad libitum but chronic nonsteroidal anti-inflammatory drug (NSAID) use was not allowed.

The primary, protocol-defined, outcome assessment measures were 1) frequency of exacerbations per patient and 2) proportion of exacerbation-free patients. A number of secondary outcome measures were also employed as described in Table 1.

In addition to clinical measures, annual magnetic resonance imaging (MRI) were performed and quantitated for extent of disease as determined by changes in total area of lesions. In a substudy of patients (N=52) at one site, MRIs were performed every 6 weeks and quantitated for disease activity as determined by changes in size and number of lesions.

Results at the protocol designated endpoint of 2 years (see Table 1):

In the 2 year analysis, there was a 31% reduction in annual exacerbation rate, from 1.31 in the placebo group to 0.9 in the 0.25 mg (8 million IU) group. The p-value for this difference was 0.0001. The proportion of patients free of exacerbations was 16% in the placebo group, compared with 25% in the BETASERON 0.25 mg (8 million IU) group.

Of the first 372 patients randomized, 72 (19%) failed to complete 2 full years on their assigned treatments. The reasons given for withdrawal varied with treatment assignment. Excessive use of steroids accounted for 11 of the 26 placebo withdrawals. In contrast, among the 21 withdrawals from the 0.05 mg (1.6 million IU) assigned group and the 25 withdrawals from the 0.25 mg (8 million IU) assigned group, excessive steroid use accounted for only three (two in the 0.05 mg [1.6 million IU] group and one in the 0.25 mg [8 million IU] group). Withdrawals for adverse events attributed to study article, however, were more common among BETASERON treated patients: 1, 5, and 10 withdrew from the placebo, 0.05 mg (1.6 million IU), and 0.25 mg (8 million IU) groups, respectively.

Table 1: 2-Year Study Results

Primary and Secondary Clinical Endpoints

Efficacy Parameters	Treatment Groups			Statistical Comparison p-value		
Primary Endpoints	**Placebo (N=123)**	**0.05 mg (1.6 mIU) (N =125)**	**0.25 mg (8 mIU) (N=124)**	**Placebo vs 0.05 mg (1.6 mIU)**	**0.05 mg (1.6 mIU) vs 0.25 mg (8 mIU)**	**Placebo vs 0.25 mg (8 mIU)**
Annual exacerbation rate	1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients†	16%	18%	25%	0.609	0.288	0.094
Exacerbation frequency per patient 0	20	22	29	0.151	0.077	0.001
1	32	31	39			
2	20	28	17			
3	15	15	14			
4	15	7	9			
≥5	21	16	8			
Secondary Clinical Endpoints††						
Median number of months to first on-study exacerbation	5	6	9	0.299	0.097	0.010
Rate of moderate or severe exacerbations per year	0.47	0.29	0.23	0.020	0.257	0.001
Mean number of moderate or severe exacerbation days per patient	44.1	33.2	19.5	0.229	0.064	0.001
Mean change in EDSS score‡ at endpoint	0.21	0.21	-0.07	0.995	0.108	0.144
Mean change in Scripps score‡‡ at endpoint	-0.53	-0.50	0.66	0.641	0.051	0.126
Median duration in days per exacerbation	36	33	35.5	ND	ND	ND
% change in mean MRI lesion area at endpoint	21.4%	9.8%	-0.9%	0.015	0.019	0.0001

ND Not done.

† 14 exacerbation-free patients (0 from placebo, 6 from 0.05 mg, and 8 from 0.25 mg) dropped out of the study before completing 6 months of therapy. These patients are excluded from this analysis.

†† Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.

‡ EDSS scores range from 0-10, with higher scores reflecting greater disability.

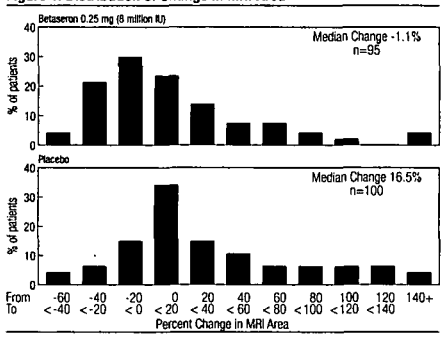
‡‡ Scripps neurologic rating scores range from 0-100, with smaller scores reflect greater disability.

Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 million IU) BETASERON-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed between the groups, with 16 in the 0.25 mg (8 million IU) BETASERON group and 15 in the placebo group. The average number of days of MS-related steroid use was 41 days in the 0.25 mg (8 million IU) BETASERON group and 55 days in the placebo group (p=0.004).

MRI data were also analyzed for patients in this study. A frequency distribution of the observed percent changes in MRI area at the end of 2 years was obtained by grouping the percentages in successive intervals of equal width. Figure 1 displays a histogram of the proportions of patients who fell into each of these intervals. The median percent change in MRI area for the 0.25 mg (8 million IU) group was -1.1% which was significantly smaller than the 16.5% observed for the placebo group (p=0.0001).

In an evaluation of frequent MRI scans (every 6 weeks) on 52 patients at one site, the percent of scans with new or expanding lesions was 29% in the placebo group and 6% in the 0.25 mg (8 million IU) treatment group (p=0.006)

Figure 1: Distribution of Change in MRI Area



MRI scanning is viewed as a useful means to visualize changes in white matter that are believed to be a reflection of the pathologic changes that, appropriately located within the central nervous system (CNS), account for some of the signs and symptoms that typify relapsing-remitting MS. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with clinical exacerbations probably because many of the lesions affect so-called "silent" regions of the CNS. Moreover, it is not clear what fraction of the lesions seen on MRI become foci of irreversible demyelinization (i.e., classic white matter plaques). The prognostic significance of the MRI findings in this study has not been evaluated.

At the end of 2 years on assigned treatment, patients in the study had the option of continuing on treatment under blinded conditions. Approximately 80% of patients under each treatment accepted. Although there was a trend toward patient benefit in the BETASERON groups during the third year, particularly in the 0.25 mg (8 million IU) group, there was no statistically significant difference between the BETASERON-treated vs. placebo-treated patients in exacerbation rate, or in any of the secondary endpoints described in Table 1. As noted above, in the 2-year analysis, there was a 31% reduction in exacerbation rate in the 0.25 mg (8 million IU) group, compared with placebo. The p-value for this difference was 0.0001. In the analysis of the third year alone, the difference between treatment groups was 28%. The p-value was 0.065. The lower number of patients may account for the loss of statistical significance, and lack of direct comparability among the patient groups in this extension study make the interpretation of these results difficult. The third-year MRI data did not show a trend toward additional benefit in the BETASERON arm compared with the placebo arm.

Throughout the clinical trial, serum samples from patients were monitored for the development of antibodies to Interferon beta-1b. In patients receiving 0.25 mg (8 million IU) of BETASERON (N=124) every other day, 45% were found to have serum neutralizing activity on at least one occasion. One third had neutralizing activity confirmed by at least two consecutive positive titres. This development of neutralizing activity may be associated with a reduction in clinical efficacy, although the exact relationship between antibody formation and therapeutic efficacy is not yet known.

INDICATIONS

BETASERON (Interferon beta-1b) is indicated for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. (See **ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials.**) Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery. The safety and efficacy of BETASERON in chronic progressive MS has not been evaluated.

CONTRAINDICATIONS

BETASERON (Interferon beta-1b) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin Human, USP, or any other component of the formulation.

WARNINGS

One suicide and 4 attempted suicides were observed among 372 study patients during a 3-year period. All five patients received BETASERON (Interferon beta-1b) (three in the 0.05 mg [1.6 million IU] group and two in the 0.25 mg [8.0 million IU] group). There were no attempted suicides in patients on study who did not receive BETASERON. Depression and suicide have been reported to occur in patients receiving interferon alpha, a related compound. Patients to be treated with BETASERON should be informed that depression and suicide ideation can be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

PRECAUTIONS

General: Patients should be instructed in injection techniques to assure the safe self-administration of BETASERON (Interferon beta-1b). (See below and **BETASERON [Interferon beta-1b] Patient Information sheet.**)

Information to be provided to the patient: Instruction on self-injection technique and procedures: It is recommended that the first injection be administered by, or under the direct supervision of, a physician. Appropriate instructions for reconstitution of BETASERON and self-injection, using aseptic techniques, should be given to the patient. A careful review of the **BETASERON [Interferon beta-1b] Patient Information** sheet is also recommended.

Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. Information on how to acquire a puncture resistant container for disposal of used needles and syringes should be given to the patient along with instructions for safe disposal of full containers.

Eighty-five percent of patients in the controlled MS trial reported injection site reactions at one or more times during therapy. In general, these were transient and did not require discontinuation of therapy, but the nature and severity of all reported reactions should be carefully assessed. Patient understanding and use of aseptic self-injection technique and procedures should be periodically reevaluated.

Flu-like symptoms are not uncommon following initiation of therapy with BETASERON. In the controlled MS clinical trial, acetaminophen was permitted for relief of fever or myalgias.

Patients should be cautioned not to change dosage or schedule of administration without medical consultation.

Awareness of adverse reaction: Patients should be advised about the common adverse events associated with the use of BETASERON, particularly, injection site reactions and the flu-like symptom complex (see **ADVERSE REACTIONS** section).

Patients should be cautioned to report depression or suicidal ideation (see **WARNINGS** section).

Patients should be advised about the abortifacient potential of BETASERON (see **PRECAUTIONS, Use in Pregnancy**).

Laboratory Tests: The following laboratory tests are recommended on patients prior to initiating BETASERON therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating BETASERON therapy. In the controlled MS trial, patients were monitored every 3 months. The study protocol stipulated that BETASERON therapy be discontinued in the event the absolute neutrophil count fell below 750/mm^3. When the absolute neutrophil count had returned to a value greater than 750/mm^3, therapy could be restarted at a 50% reduced dose. No patients were withdrawn or dose reduced for neutropenia or lymphopenia.

Similarly, if hepatic transaminase (SGOT/SGPT) levels exceeded 10 times the upper limit of normal, or if the serum bilirubin exceeded 5 times the upper limit of normal, therapy was discontinued. In each instance during the controlled MS trial, hepatic enzyme abnormalities returned to normal following discontinuation of therapy. When measurements had decreased to below these levels, therapy could be restarted at a 50% dose reduction, if clinically appropriate. Two patients were dose reduced for increased liver enzymes; one continued on treatment and one was ultimately withdrawn.

Drug Interactions: Interactions between BETASERON and other drugs have not been fully evaluated. Although studies designed to examine drug interactions have not been done, it was noted that corticosteroid or ACTH treatment of relapses for periods of up to 28 days has been administered to patients (N=180) receiving BETASERON.

BETASERON administered in three cancer patients over a dose range of 0.025 mg (0.8 million IU) to 2.2 mg (71 million IU) led to a dose-dependent inhibition of antipyrine elimination. The effect of alternate-day administration of 0.25 mg (8 million IU) of BETASERON on drug metabolism in MS patients is unknown.

Impairment of Fertility: Studies in rhesus monkeys at doses up to 0.33 mg (10.7 million IU)/kg/day (32 times the

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recommended human dose based on body surface area comparison)* In normally cycling rhesus female monkeys had no apparent adverse effects on the menstrual cycle or on associated hormonal profiles (progesterone and estradiol) when administered over 3 consecutive menstrual cycles. The extrapolability of animal doses to human doses is not known. Effects of BETASERON on normal cycling human females are not known. *body surface dose based on 70-kg female

Use in Pregnancy: Pregnancy Category C: BETASERON was not terato-genic at doses up to 0.42 mg (13.3 million IU)/kg/day in rhesus monkeys, but demonstrated a dose-related abortifacient activity when administered at doses ranging from 0.028 mg (0.89 million IU)/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 million IU)/kg/day (40 times the recommended human dose based on body surface area comparison). The extrapolability of animal doses to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in patients (N=4) who participated in the BETASERON MS clinical trial. BETASERON given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects, however, it is not known if teratogenic effects exist in humans. There are no adequate and well controlled studies in pregnant women. Women of childbearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking BETASERON, the patient should discontinue therapy.

Nursing Mothers: It is not known whether BETASERON is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BETASERON, a decision should be made as to whether either to discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

Pediatric Use: Safety and efficacy in children under 18 years of age have not been established.

Dependence Liability: No evidence or experience suggests that abuse or dependence occurs with BETASERON therapy; however, the risk of dependence has not been systematically evaluated.

ADVERSE REACTIONS

Experience with BETASERON (Interferon beta-1b) in patients with MS is limited to a total of 147 patients at the recommended dose of 0.25 mg (8 million IU) every other day or more. Consequently, adverse events that are associated with the use of BETASERON in MS patients at a low incidence of 1% or less may not have been observed in premarketing studies. Clinical experience with BETASERON in other populations (patients with cancer, HIV positive patients, etc.) provides some degree of added reassurance; however, experience in non-MS populations may not be fully applicable to the MS population.

Injection site reactions (85%) and injection site necrosis (5%) occurred after administration of BETASERON. Inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated ($p<0.05$) with the 0.25 mg (8 million IU) BETASERON-treated group. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7 days per year. Three patients withdrew from the 0.25 mg (8 million IU) BETASERON-treated group for injection site pain.

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 million IU) BETASERON. A patient was defined as having a flu-like symptom complex if flu-like symptoms or at least two of the following symptoms were concurrently reported: fever, chills, myalgia, malaise or sweating. Only myalgia, fever, and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 51% of patients experiencing the event during the first 3 months of treatment compared to 4% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3 days and the median duration per patient was 10.4 days per year.

Laboratory abnormalities included:

- absolute neutrophil count less than 1500/mm^3 (18%) (no patients had absolute neutrophil counts less than 500/mm^3)
- WBC less than 3000/mm^3 (16%)
- lymphocyte count less than 1500/mm^3 (82%)
- SGPT greater than 5 times baseline value (19%)
- total bilirubin greater than 2.5 times baseline value (6%).

Three patients were withdrawn from treatment with 0.25 mg (8 million IU) BETASERON for abnormal liver enzymes including one following dose reduction (see **PRECAUTIONS, Laboratory Tests**).

Twenty-one (28%) of the 76 females, of childbearing age, treated at 0.25 mg (8 million IU) BETASERON and 10 (13%) of the 76 females, of child-bearing age, treated with placebo reported menstrual disorders. All of these reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

Mental disorders have been observed in patients in this study. Symptoms included depression, anxiety, emotional lability, depersonalization, suicide attempts, confusion, etc. In the treatment group, two patients withdrew for confusion. One suicide and four attempted suicides were also reported. It is not known whether these symptoms may be related to the underlying neuro-logical basis of MS, to BETASERON treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be closely monitored and cessation of therapy considered.

Additional common adverse clinical and laboratory events associated with the use of BETASERON are listed in the following paragraphs. These events occurred at an incidence of 5% or more in the 124 MS patients treated with 0.25 mg (8 million IU) of BETASERON every other day for periods of up to 3 years in the controlled trial, and at an incidence that was at least twice that observed in the 123 placebo patients.

Common adverse clinical and laboratory events associated with the use of BETASERON were:

- injection site reaction (85%),
- injection site necrosis (5%),
- flu-like symptoms (53%),
- palpitation (8%),
- hypertension (7%),
- tachycardia (6%),
- peripheral vascular disorders (5%),
- gastrointestinal disorders (6%),
- absolute neutrophil count <1500/mm^3 (18%),
- WBC <3000/mm^3 (16%),
- lymphocyte count <1500/mm^3 (82%),
- SGPT >5 times baseline value (19%),
- total bilirubin >2.5 times baseline value (6%),
- somnolence (6%),
- dyspnea (8%),
- laryngitis (6%),
- menstrual disorder (17%),
- cystitis (8%),
- breast pain (7%),
- pelvic pain (6%), and
- menorrhagia (6%).

A total of 277 MS patients have been treated with BETASERON in doses ranging from 0.025 mg (0.8 million IU) to 0.5 mg (16 million IU). During the first 3 years of treatment, withdrawals due to clinical adverse events or laboratory abnormalities not mentioned above included:

- fatigue (2%, 6 patients)
- cardiac arrhythmia (<1%, 1 patient)
- allergic urticarial skin reaction to injections (<1%, 1 patient)
- headache (<1%, 1 patient)
- unspecified adverse events (<1%, 1 patient)
- "felt sick" (<1%, 1 patient)

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 million IU) BETASERON every other day for periods of up to 3 years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been reclassified using the standard COSTART glossary to reduce the total number of terms employed in the table. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

Table 2: Adverse Events and Laboratory Abnormalities

Adverse Reaction	Placebo N=123	0.25 mg (8 mIU) N=124
Body as a Whole		
- Injection site reaction*	37%	85%
- Headache	77%	84%
- Fever*	41%	59%
- Flu-like symptom complex*	56%	76%
- Pain	48%	52%
- Asthenia*	35%	49%
- Chills*	19%	46%
- Abdominal pain	24%	32%
- Malaise*	3%	15%
- Generalized edema	6%	8%
- Pelvic pain	3%	6%
- Injection site necrosis*	0%	5%
- Cyst	2%	4%
- Necrosis	0%	2%
- Suicide attempt	0%	2%
Cardiovascular System		
- Migraine	7%	12%
- Palpitation*	2%	8%
- Hypertension	2%	7%
- Tachycardia	3%	6%
- Peripheral vascular disorder	2%	5%
- Hemorrhage	1%	3%
Digestive System		
- Diarrhea	29%	35%
- Constipation	18%	24%
- Vomiting	19%	21%
- Gastrointestinal disorder	3%	6%
Endocrine System		
- Goiter	0%	2%
Hemic and Lymphatic System		
- Lymphocytes < 1500/mm^3	67%	82%
- ANC < 1500/mm^3*	6%	18%

Table 2: Adverse Events and Laboratory Abnormalities (cont'd)

Adverse Reaction	Placebo N=123	0.25 mg (8 mIU) N=124
Hemic and Lymphatic System (cont'd)		
- WBC < 3000/mm^3*	5%	16%
- Lymphadenopathy	11%	14%
Metabolic and Nutritional Disorders		
- SGPT > 5 times baseline*	6%	19%
- Glucose < 55 mg/dL	13%	15%
- Total bilirubin > 2.5 times baseline	2%	6%
- Urine protein > 1+	3%	5%
- SGOT > 5 times baseline*	0%	4%
- Weight gain	0%	4%
- Weight loss	2%	4%
Musculoskeletal System		
- Myalgia*	28%	44%
- Myasthenia	10%	13%
Nervous System		
- Dizziness	28%	35%
- Hypertonia	24%	26%
- Depression	24%	25%
- Anxiety	13%	15%
- Nervousness	5%	8%
- Somnolence	3%	6%
- Confusion	2%	4%
- Speech disorder	1%	3%
- Convulsion	0%	2%
- Hyperkinesia	0%	2%
- Amnesia	0%	2%
Respiratory System		
- Sinusitis	26%	36%
- Dyspnea*	2%	8%
- Laryngitis	2%	6%
Skin and Appendages		
- Sweating*	11%	23%
- Alopecia	2%	4%
Special Senses		
- Conjunctivitis	10%	12%
- Abnormal vision	4%	7%
Urogenital System		
- Dysmenorrhea	11%	18%
- Menstrual disorder*	8%	17%
- Metrorrhagia	8%	15%
- Cystitis	4%	8%
- Breast pain	3%	7%
- Menorrhagia	3%	6%
- Urinary urgency	2%	4%
- Fibrocystic breast	1%	3%
- Breast neoplasm	0%	2%

* Significantly associated with BETASERON treatment

It should be noted that the figures cited in the table cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. The cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studies.

Other events observed during premarketing evaluation of various doses of BETASERON in 1440 patients are listed in the paragraphs that follow. Because most of the events were observed in open and uncontrolled studies, the role of BETASERON in their causation cannot be reliably determined.

Body as a Whole: abscess, adenoma, anaphylactoid reaction, ascites, cellulitis, hernia, hydrocephalus, hypothermia, infection, peritonitis, photosensitivity, sarcoma, sepsis, and shock;

Cardiovascular System: angina pectoris, arrhythmia, atrial fibrillation, cardiomegaly, cardiac arrest, cerebral hemorrhage, cerebral ischemia, endocarditis, heart failure, hypotension, myocardial infarct, pericardial effusion, postural hypotension, pulmonary embolus, spider angioma, subarachnoid hemorrhage, syncope, thrombophlebitis, thrombosis, varicose vein, vasospasm, venous pressure increased, ventricular extrasystoles, and ventricular fibrillation;

Digestive System: aphthous stomatitis, cardiospasm, cheilitis, cholecystitis, cholelithiasis, duodenal ulcer, dry mouth, enteritis, esophagitis, fecal impaction, fecal incontinence, flatulence, gastritis, gastrointestinal hemorrhage, gingivitis, glossitis, hematemesis, hepatic neoplasia, hepatitis, hepatomegaly, ileus, increased salivation, intestinal obstruction, melena, nausea, oral leukoplakia, oral moniliasis, pancreatitis, periodontal abscess, proctitis, rectal hemorrhage, salivary gland enlargement, stomach ulcer, and tenesmus;

Endocrine System: Cushing's Syndrome, diabetes insipidus, diabetes mellitus, hypothyroidism, and inappropriate ADH;

Hemic and Lymphatic System: chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/mm^3, and splenomegaly;

Metabolic and Nutritional Disorders: alcohol intolerance, alkaline phosphatase greater than 5 times baseline value, BUN greater than 40 mg/dL, calcium greater than 11.5 mg/dL, cyanosis, edema, glucose greater than 160 mg/dL, glycosuria, hypoglycemic reaction, hypoxia, ketosis, and thirst;

Musculoskeletal System: arthritis, arthrosis, bursitis, leg cramps, muscle atrophy, myopathy, myositis, ptosis, and tenosynovitis;

Nervous System: abnormal gait, acute brain syndrome, agitation, apathy, aphasia, ataxia, brain edema, chronic brain syndrome, coma, delirium, delusions, dementia, depersonalization, diplopia, dystonia, encephalopathy, euphoria, facial paralysis, foot drop, hallucinations, hemiplegia, hypalgesia, hyperesthesia, incoordination, intracranial hypertension, libido decreased, manic reaction, meningitis, neuralgia, neuropathy, neurosis, nystagmus, oculogyric crisis, ophthalmoplegia, papilledema, paralysis, paranoid reaction, psychosis, reflexes decreased, stupor, subdural hematoma, torticollis, tremor and urinary retention;

Respiratory System: apnea, asthma, atelectasis, carcinoma of the lung, hemoptysis, hiccup, hyperventilation, hypoventilation, interstitial pneumonia, lung edema, pleural effusion, pneumonia, and pneumothorax;

Skin and Appendages: contact dermatitis, erythema nodosum, exfoliative dermatitis, furunculosis, hirsutism, leukoderma, lichenoid dermatitis, maculopapular rash, psoriasis, seborrhea, skin benign neoplasm, skin carcinoma, skin hypertrophy, skin necrosis, skin ulcer, urticaria, and vesiculobullous rash;

Special Senses: blepharitis, blindness, deafness, dry eyes, ear pain, iritis, keratoconjunctivitis, mydriasis, otitis externa, otitis media, parosmia, photophobia, retinitis, taste loss, taste perversion, and visual field defect;

Urogenital System: anuria, balanitis, breast engorgement, cervicitis, epididymitis, gynecomastia, hematuria, impotence, kidney calculus, kidney failure, kidney tubular disorder, leukorrhea, nephritis, nocturia, oliguria, polyuria, salpingitis, urethritis, urinary incontinence, uterine fibroids enlarged, uterine neoplasm, and vaginal hemorrhage.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS USE ONLY

The recommended dose of BETASERON (Interferon beta-1b) for the treatment of ambulatory relapsing-remitting MS is 0.25 mg (8 million IU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose are presented above (see **CLINICAL PHARMACOLOGY, Clinical Trials**).

Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from a 2-year, double-blind, placebo-controlled clinical trial (see **CLINICAL PHARMACOLOGY, Clinical Trials**). Safety data is not available beyond the third year. Some patients were discontinued from this trial after 6 months or more, due to a perceived increase in disease activity or progression.

To reconstitute lyophilized BETASERON for injection, use a sterile syringe and needle to inject 1.2 mL of the diluent supplied, Sodium Chloride, 0.54% Solution, into the BETASERON vial. Gently swirl the vial of BETASERON to dissolve the drug completely; do not shake. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with accompanying diluent, each mL of solution contains 0.25 mg (8 million IU) Interferon beta-1b, 13 mg Albumin Human USP and 13 mg Dextrose USP.

Withdraw 1 mL of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include abdomen, buttocks and thighs. A vial is suitable for single use only; unused portions should be discarded 3 hours after reconstitution. (See **BETASERON (Interferon beta-1b) Patient Information** sheet for **self-injection procedure**.)

PHARMACEUTICAL INFORMATION

Common Name:	Interferon beta-1b (USAN)
Molecular Weight:	approximately 18,500 daltons
Physical Form:	sterile, lyophilized powder
Composition (each vial contains):	0.3 mg (9.6 million IU), 15 mg Albumin Human USP, 15 mg Dextrose USP
Stability (before reconstitution):	Stable for 24 months when stored under refrigeration at 2° to 8°C (36° to 46°F). Avoid freezing.
Stability (after reconstitution):	The reconstituted product contains no preservative. Product should be used within 3 hours of reconstitution. Store under refrigeration at 2° to 8°C (36° to 46°F). Avoid freezing.

AVAILABILITY OF DOSAGE FORMS

BETASERON (Interferon beta-1b) is presented as a 3 mL single-use vial of lyophilized powder containing 0.3 mg (9.6 million IU) of Interferon beta-1b, 15 mg Albumin Human USP, and 15 mg Dextrose USP. BETASERON is supplied in cartons containing 15 vials of medication and 15 vials of diluent (2 mL of Sodium Chloride, 0.54% Solution). Store under refrigeration at 2° to 8°C (36° to 46°F).

Product Monograph available on request.

1. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43: 655-661.

2. Paty DW, Li DKB, the UBC MS/MRI Study Group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43: 662-667. PAAB

3. Data on File, Reid/Fragner confirmations, June 1995. PMAC

See pages iv, v.

Lamotrigine

Lamictal®

Lamotrigine Tablets
(25, 100, 150 mg)
Antiepileptic

ACTION AND CLINICAL PHARMACOLOGY

LAMICTAL (lamotrigine) is a drug of the phenyltriazine class chemically unrelated to existing antiepileptic drugs (AEDs). Lamotrigine is thought to act at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit 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 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 antiepileptic drug therapy in adult patients with partial seizures, with or without generalized tonic-clonic seizures, that are not satisfactorily controlled.

Pharmacokinetics Adults: LAMICTAL is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 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 (C_{max}=0.6 - 4.6 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 ($t_{1/2}$) and volume of distribution (Vd/F) are independent of dose. The $t_{1/2}$ averages 33 hours after single doses and Vd/F ranges from 0.9 to 1.4 L/kg. Following repeated dosing in healthy volunteers for 14 days, the $t_{1/2}$ decreased by an average of 26% (mean steady state $t_{1/2}$ of 26.4 hours) and plasma clearance increased by an average of 33%. In a single-dose study where healthy volunteers were administered both oral and intravenous doses of lamotrigine, the absolute bioavailability of oral lamotrigine was 98%.

Lamotrigine 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.

Lamotrigine 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 β-glucuronidase. Approximately 70% of an oral LAMICTAL dose is recovered in urine 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 individuals with chronic renal failure (with mean creatinine clearance of 13 mL/min) who were not receiving other antiepileptic 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.

Gilbert's Syndrome: Gilbert's syndrome (idiopathic unconjugated hyperbilirubinemia) does not appear to affect the pharmacokinetic profile of lamotrigine.

Concomitant Antiepileptic Drugs: In patients with epilepsy, concomitant administration of LAMICTAL with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone or phenobarbital) decreases the mean lamotrigine $t_{1/2}$ to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases $t_{1/2}$ and decreases the clearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong $t_{1/2}$ up to approximately 27 hours. Acetaminophen was shown to slightly decrease the $t_{1/2}$ and increase the clearance 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		Patients with Epilepsy		
	LAMICTAL Administered	LAMICTAL	LAMICTAL+ Valproic Acid[2]	LAMICTAL +Enzyme-Inducing AEDs	LAMICTAL+ Valproic Acid	LAMICTAL+ Valproic Acid +Enzyme-Inducing AEDs
T_{max} (hrs)	Single Dose	2.2 (0.25–12.0)[1]	1.8 (1.0–4.0)	2.3 (0.5–5.0)	4.8 (1.8–8.4)	3.8 (1.0–10.0)
	Multiple Dose	1.7 (0.5–4.0)	1.9 (0.5–3.5)	2.0 (0.75–5.93)	ND	ND
$t_{1/2}$	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 (41.9–113.5)	12.6 (7.5–23.1)	ND	ND
Plasma Clearance (mL/min/kg)	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)
	Multiple Dose	0.58 (0.24–1.15)	0.18 (0.12–0.33)	1.21 (0.66–1.82)	ND	ND

ND=Not done
1. Range of individual values across studies
2. 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 at this time.

CONTRAINDICATIONS

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

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 titration dosing and use of concomitant valproic acid 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 syndrome, 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 initiating event in one reported death.

It is recommended that the physician closely monitor (including hepatic, renal and clotting parameters) patients who acutely develop any combination of unexplained rash, fever, flu-like 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 a skin rash in clinical trials 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 therapy with LAMICTAL must be weighed against the increased risk of serious rash in patients who have already developed a rash.

PRECAUTIONS

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 (lamotrigine) 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 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 valproic acid (VPA), particularly in the absence of enzyme-inducing AEDs. 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[1]	1788	9.2%	1.8%	0.1%
Enzyme-Inducing AEDs[1] + VPA	318	8.8%	3.5%	0.9%
VPA ±Non-Enzyme-Inducing AEDs[2]	159	20.8%	11.9%	2.5%
Non-Enzyme-Inducing AEDs[2]	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 Dose[1] of LAMICTAL in the Presence of Concomitant AEDs, on the Incidence of Rash Leading to Withdrawal of Treatment in Add-On Clinical Trials

AED Group	Enzyme-Inducing AEDs[2]		Enzyme-Inducing AEDs[2] + VPA		VPA ± Non-Enzyme-Inducing AEDs[3]	
LAMICTAL Average Daily Dose (mg)	Total Patient Number	Percentage of Patients Withdrawn	Total Patient Number	Percentage of Patients Withdrawn	Total Patient Number	Percentage of Patients 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	1.4	179	4.5	15	40.0
≥125	601	2.8	11	18.2	0	0.0

1. Average daily dose in week 1
2. Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone
3. Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, 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

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, carbamazepine, phenobarbital, primidone) increase the plasma clearance and reduce the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY).

Valproic acid reduces the plasma clearance and prolongs 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 ethinylestradiol 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 menstrual bleeding pattern.

Drugs Depressing Cardiac Conduction: (see Patients with Special Diseases and Conditions).

Drug/Laboratory Test Interactions: LAMICTAL has not been associated with any assay interferences in clinical laboratory tests.

Use in the Elderly The safety and efficacy of LAMICTAL in elderly patients with epilepsy have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly 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

Pregnancy: Studies in mice, rats and rabbits given lamotrigine orally or intravenously revealed no evidence of teratogenicity; 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 folate concentrations in adults; however, its effects during human fetal development are unknown.

Labor and Delivery: The effect of LAMICTAL on 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-feeding 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.

Renal Failure: A study in individuals with chronic renal failure (not receiving other AEDs) indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY). 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 conduction.

Dependence Liability 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 clinical laboratory parameters or plasma levels of concomitant AEDs.

ADVERSE REACTIONS

Adverse experiences in patients receiving LAMICTAL (lamotrigine) 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 daily 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 PRECAUTIONS, Skin-Related Events, Table 2).

Associated with Discontinuation of Treatment In controlled clinical trials, 6.9% of the 711 patients receiving LAMICTAL discontinued therapy due to an adverse experience, 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, headache, ataxia, nausea, diplopia, somnolence, seizure exacerba-

tion, asthenia, 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 half 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 Table 4 enumerates 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* clinical 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 recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of adverse experiences into a smaller number of standardized event categories.
Since the adverse experiences reported occurred during treatment with LAMICTAL in combination with other antiepileptic 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[1]

Body System/ Adverse Experience[2]	Percent of Patients Receiving LAMICTAL (and other AEDs) (n=711)	Percent of Patients Receiving Placebo (and other AEDs) (n=419)	Percent of Patients Receiving LAMICTAL (and other AEDs) Who Were Discontinued (n=711)
BODY AS A WHOLE			
Headache	29.1	19.1	1.3
Accidental Injury	9.1	8.6	0.1
Asthenia	8.6	8.8	0.3
Flu Syndrome	7.0	5.5	0.0
Pain	6.2	2.9	0.1
Back Pain	5.8	6.2	0.0
Fever	5.5	3.6	0.1
Abdominal Pain	5.2	3.6	0.1
Infection	4.4	4.1	0.0
Neck Pain	2.4	1.2	0.0
Malaise	2.3	1.9	0.3
Seizure Exacerbation	2.3	0.5	0.3
DIGESTIVE			
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
Arthralgia	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	5.6	1.9	0.4
Tremor	4.4	1.4	0.0
Depression	4.2	2.6	0.0
Anxiety	3.8	2.6	0.0
Convulsion	3.2	1.2	0.3
Irritability	3.0	1.9	0.1
Speech Disorder	2.5	0.2	0.1
Memory Decreased	2.4	1.9	0.0
RESPIRATORY			
Rhinitis	13.6	9.3	0.0
Pharyngitis	9.8	8.8	0.0
Cough Increased	7.5	5.7	0.0
Respiratory Disorder	5.3	5.5	0.1
SKIN AND APPENDAGES			
Rash	10.0	5.0	1.1
Pruritus	3.1	1.7	0.3
SPECIAL SENSES			
Diplopia	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

1. 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.
2. Adverse experiences reported by at 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 clinical 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 multiforme, esophagitis, hematemesis, hemolytic anemia, 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 frequent monitoring 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 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 elimination half-life of lamotrigine by 50% and double the plasma clearance; conversely, valproic acid more than doubles the elimination half-life of lamotrigine and reduces the plasma clearance by 50% (see ACTION AND CLINICAL PHARMACOLOGY). These clinically important interactions require dosage schedules of LAMICTAL as 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 change 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. In controlled clinical studies, doses of LAMICTAL that were efficacious generally produced steady-state trough plasma lamotrigine concentrations of 1 to 4 μg/mL in patients receiving one or more concomitant AEDs. Doses of LAMICTAL producing this plasma concentration range were well tolerated. As with any antiepileptic drug, the oral dose of LAMICTAL should be adjusted to the needs of the individual *patient, taking into consideration the concomitant AED therapy the patient is receiving.*

Table 5 LAMICTAL Recommended Dosage Schedule for Adults

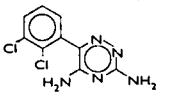
Treatment Week	Patients Taking: Enzyme-Inducing AEDs[1] *Without* Valproic Acid	Patients Taking: Enzyme-Inducing AEDs[1] *With* Valproic Acid	For Information*: Patients Taking *Valproic Acid Only*
Weeks 1 + 2	50 mg once a day	25 mg once a day	25 mg every other day
Weeks 3 + 4	50 mg twice a day	25 mg 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 day

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

* Column 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 therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. 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 initial titration dose of 12.5 mg daily (see PRECAUTIONS, Skin Related Events, Table 3; see also WARNINGS). 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 clinically indicated, titration dosing should proceed with extreme caution, especially during the first six weeks of dose titration.
Withdrawal of Concomitant AEDs: In patients receiving LAMICTAL who have all concomitant enzyme-inducing AEDs withdrawn, the $t_{1/2}$ of lamotrigine will be approximately doubled (see ACTION AND CLINICAL PHARMACOLOGY). Under these conditions, it may be necessary to reduce the dose of LAMICTAL. In contrast, in patients receiving LAMICTAL who have valproic acid withdrawn, the $t_{1/2}$ of lamotrigine will be decreased; under these conditions, it may be necessary to increase the dose of LAMICTAL.
Geriatric Patients: There is little experience with the use of LAMICTAL in elderly patients. Caution 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 lamotrigine 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.
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.
Children Dosage recommendations for children under 18 years of age are not yet established.

PHARMACEUTICAL INFORMATION
Drug Substance
Brand Name: LAMICTAL
Common Name: Lamotrigine
Chemical Name: 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-[USAN]
Chemical Name: 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine [Chem. Abstr.]
Structural Formula:[USAN]



Molecular Formula: $C_9H_7Cl_2N_5$ Molecular Weight: 256.09
Description: Lamotrigine is a white to pale cream powder. The pK_a at 25°C is 5.7. It is practically insoluble in water (0.017% w/v); slightly soluble in ethanol (0.41% w/v), chloroform (0.11% w/v) and octanol (0.28% w/v).

Composition
LAMICTAL Tablets contain lamotrigine and the following non-medicinal ingredients:
- cellulose, 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 room temperature (15°C to 30°C) in a dry place and protected from light.

AVAILABILITY OF DOSAGE FORMS
LAMICTAL Tablets are available in three different strengths: LAMICTAL Tablets 25 mg: White, scored, shield-shaped tablets engraved with "LAMICTAL" and "25". Bottles of 100.
LAMICTAL Tablets 100 mg: Peach, scored, shield-shaped tablets engraved with "LAMICTAL" and "100". Bottles of 100.
LAMICTAL Tablets 150 mg: Cream, scored, shield-shaped tablets engraved with "LAMICTAL" and "150". Bottles of 60.

Product Monograph available to health professionals upon request.

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See pages vi, vii, viii, ix.

PRESCRIBING INFORMATION

SABRIL®
VIGABATRIN

Tablets
500 mg

Antiepileptic

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 refractory 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 related 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 dose- and 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 microvacuolation occurred *in utero*. The possibility that microvacuolation 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	261	12.5
headache	80	3.8
dizziness	79	3.8
nervousness	56	2.7
depression	52	2.5
memory disturbances	47	2.3
diplopia	46	2.2
aggression	42	2.0
ataxia	39	1.9
vertigo	39	1.9
hyperactivity	37	1.8
vision abnormal	34	1.6
confusion	29	1.4
insomnia	26	1.3
impaired concentration	25	1.2
personality disorder	23	1.1
agitation	21	1.0
Digestive		
abdominal pain	34	1.6
constipation	29	1.4
vomiting	28	1.4
nausea	28	1.4
Body as a Whole		
fatigue	192	9.2
weight gain	104	5.0
asthenia	23	1.1

Adverse events reported with a frequency of less than 1% include: anxiety, 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	24	8.0
hyperkinesia	23	7.7
aggression	8	2.7
insomnia	8	2.7
agitation	7	2.3
ataxia	7	2.3
emotional lability	3	1.0
headache	3	1.0
increased seizures	3	1.0
Digestive		
vomiting	6	2.0
nausea	3	1.0
increased saliva	3	1.0
Body as a Whole		
weight gain	9	3.0
fatigue	8	2.7
hypotonia	3	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 - 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.

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AVAILABILITY OF DOSAGE FORMS

Tablets Each SABRIL (vigabatrin) 500 mg tablet is white to off-white 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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ADVERTISERS INDEX

See pages ibc, iii.

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IMITREX®

(sumatriptan succinate)
100 mg Tablet
6 mg Subcutaneous Injection and Autoinjector

THERAPEUTIC CLASSIFICATION

Migraine Therapy

PHARMACOLOGIC CLASSIFICATION

5-HT_1-like Receptor Agonist

CLINICAL PHARMACOLOGY

IMITREX (sumatriptan succinate) is a selective 5-hydroxytryptamine$_1$-like (5-HT_1-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 carotid 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 mechanism 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-HT_1-like receptors 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_2 or 5-HT_3 receptor subtypes. Clinical response begins 10-15 minutes following subcutaneous injection and around 30 minutes following oral administration.

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_2 receptors. However, 5-HT_1-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 µg/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.

Pharmacokinetics: Sumatriptan is rapidly absorbed after oral and subcutaneous administration with a mean bioavailability of 96% after subcutaneous dosing and 14% after oral dosing. The low oral bioavailability is mainly due to hepatic metabolism and, to a lesser extent, to incomplete absorption. The oral absorption of sumatriptan is not significantly affected either during migraine attacks or by food. Following an oral dose of 100 mg, a mean C_{max} of 54 ng/mL was attained, while the time to peak plasma level was variable (0.5- 5 hours). However, 70% to 80% of C_{max} values were attained within 30-45 minutes of oral dosing. The 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 C_{max} 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 urine where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no known5-HT_1 or 5-HT_2 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 pharmacokinetic 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 or without aura. Sumatriptan is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic or basilar migraine.

CONTRAINDICATIONS: IMITREX (sumatriptan succinate) is contraindicated in patients with known hypersensitivity to any of the components of the formulation. Sumatriptan is contraindicated in patients with ischaemic heart disease, angina pectoris including Prinzmetal angina (coronary 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 patients is not recommended.

Sumatriptan has been associated with transient chest pain and tightness 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 severe or persistent and are consistent with angina, appropriate investigations 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. Sumatriptan should be used with caution in patients in whom there is a concern of ischaemic heart disease, as well as in patients with arteriosclerotic diseases such as peripheral and/or cerebral vascular disease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia and myocardial infarction, as well as transient ischaemic ST wave elevations associated with IMITREX injection. Consideration should be given to administering the first dose of Imitrex 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 CAD (hypertension, hypercholesterolaemia, obesity, diabetes, smoking, or strong family history of CAD). Sumatriptan injection should never be given intravenously. 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 present 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 cervico-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 therapeutic 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, flunarizine, 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 disease, known to be susceptible to coronary artery vasospasm, 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, ventricular tachycardia, myocardial infarction, and transient ischaemic ST elevation associated with IMITREX injection (see WARNINGS).

Incidence of Drug Related Adverse Events in Controlled Clinical Trials

Event	Tablets N=1456	Placebo N=296	S.C. Injection N=2665	Placebo N=868
Gastrointestinal:				
nausea/vomiting	12%	4%	8%	4%
gastric symptoms, abdominal discomfort	1%	≤1%	1%	<1%
dysphagia	1%	0%	1%	0%
gastro-oesophageal reflux, diarrhea and abnormal stools	<1%	≤1%	<1%	0%
Neurological:				
tingling	1%	<1%	9%	2%
malaise/fatigue	8%	2%	2%	<1%
dizziness/vertigo	5%	2%	8%	3%
warm/hot sensation	1%	<1%	8%	3%
burning sensation	<1%	0%	5%	<1%
numbness	1%	<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%	<1%
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%
Musculoskeletal:				
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 minutes 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 sumatriptan 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 concentration 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 recommended that sumatriptan be given as early as possible after the onset of aura 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, analgesic medication other than ergotamine-containing preparations may be used for further pain relief. Sumatriptan may be taken for subsequent 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 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 non-responder. Rescue medication excepting ergotamine-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 an additional 100 mg dose of sumatriptan. The maximum dose in 24 hours is 3 x 100 mg tablets (300 mg). Patients who do not respond to the first dose should not take a second dose of sumatriptan for the same attack. Sumatriptan may be taken for subsequent attacks. The tablet should be swallowed whole with water, not crushed or chewed.

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 sumatriptan. If a patient has not responded within 2 hours, he/she is considered to be a non-responder. Rescue medication excepting ergotamine-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 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 (sumatriptan succinate) Tablets are pink, film-coated tablets available in blister packs containing 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 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.

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 1993;20:131-137.* **2.** Schoenen J et al. Self-treatment of acute migraine with subcutaneous 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©, Glaxo 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 Subcutaneous 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, aspirin and caffeine (BAC) detoxification in headache patients. *Headache* 1990;30:491-496. **7.** Tansey MJB et al. Long-term experience with sumatriptan in the treatment of migraine. *Eur Neurol* 1993;33:310-315. **8.** Sullivan JT et al. Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992;52:635-642. **9.** Salonen 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 Research, 1994. **12.** Variation in Migraine Severity. Data on file. Glaxo Canada Inc., 1994.

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IMITREX®

SUMATRIPTAN SUCCINATE

See pages x, xi.

MOVEMENT DISORDER NEUROLOGIST

The Department of Neurosciences at the Sir Mortimer B. Davis Jewish General Hospital (Montreal, Quebec, Canada) is offering a full-time academic position for a Board Certified Neurologist (Canada or USA) with at least one year subspecialty training in Movement Disorders. The candidate will enter as Assistant Professor in Neurology with possibility for tenure at McGill University (Montreal). As Director of a large Parkinson's Disease Clinic at our institution, the candidate will be responsible for initiation of clinical drug trials, coordination of multi-disciplinary patient care, and supervision of resident and student teaching. Excellent opportunities are also available for basic research collaboration with the Bloomfield Centre for Research in Aging at the Lady Davis Institute for Medical Research.

Applicants should send a CV and three letters of reference to:

Dr. Calvin Melmed,
Neurologist-in-Chief,
Sir Mortimer B. Davis Jewish General Hospital
3755 Cote Ste. Catherine Road
Montreal, Quebec, Canada H3T 1E2

ACADEMIC APPOINTMENT UNIVERSITY OF SASKATCHEWAN, Neurosurgeon

The Department of Surgery invites application for a full-time appointment in the Division of Neurosurgery. The successful candidate will be appointed to the active staff of the Department of Surgery at Royal University Hospital, one of the hospitals of the Saskatoon District Health Board, and hold a full-time faculty appointment with the College of Medicine at the University of Saskatchewan. The candidate must be certified in Neurosurgery by the Royal College of Physicians and Surgeons of Canada. Applicants should have additional training and a minimum of two years' experience in cerebrovascular surgery. The successful candidate will participate in the clinical and educational activities of the Division.

The University of Saskatchewan is committed to the principles of employment equity and welcomes members of visible minorities, and people with disabilities are invited to identify themselves as members of these designated groups on their applications. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents.

Interested candidates should submit a letter of application, current curriculum vitae and names of three references to:

Dr. R.G. Keith, Chairman , Department of Surgery
University of Saskatchewan,
Royal University Hospital,
Saskatoon SK S7N 0W8

Deadline: December 31, 1995

LOCUM TENENS NEEDED!

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Busy Adult Neurology clinically orientated private practice, close to the three major hospitals, including Royal University Hospital, University of Saskatchewan.

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- Excellent opportunity with potential for future partnership

Contact:
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#408, 333, 25th Street East
Saskatoon, Saskatchewan S7K 3J8
Phone: (306) 652-1312
Fax: (306) 665-1220

1996 CSCN EEG EXAMINATIONS

To assure and maintain a high standard of competence in clinical electroencephalography across Canada, the Canadian Society of Clinical Neurophysiologists (CSCN) conducts an annual examination in EEG and related subjects for those eligible physicians entering EEG practise who elect to take it. Successful candidates will be given a certificate by the CSCN. The Provincial Licensing Bodies and the Royal College of Physicians and Surgeons of Canada have been informed of this examination and of the objective of the CSCN to maintain high standards in the practise of Clinical Neurophysiology in Canada.

Eligibility:

1. M.D. degree from a medical school approved by the CSCN.
2. At least six months of EEG training.

Format:

Written Examination - **Monday, June 24, 1996, London, Ontario**
3-hour, 100 question multiple choice and short answer

Oral Examination - **Tuesday, June 25, 1996, London, Ontario**

Language: The written and oral will be offered in both English and French.

Application: Please apply by letter to:

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

DEADLINE WITH APPLICATION FEE: MAY 1, 1996.

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INFORMATION FOR AUTHORS

The Canadian Journal of Neurological Sciences publishes original articles in neurology, neurosurgery and basic neurosciences. Manuscripts are considered for publication with the understanding that they, or the essence of their content, have not been published elsewhere except in abstract form and are not under simultaneous consideration by another journal. Articles undergo peer review. Manuscripts should be submitted to:

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Manuscript Preparation

• Submit five high quality copies of the manuscript and original illustrations. Papers will be accepted in English or French. Manuscripts must be double spaced throughout including references, tables and legends for illustrations. Margins of at least 25mm should be left on all sides.

• After a paper has been reviewed, the author will be requested to submit four copies of the revised manuscript, including illustrations and a computer diskette (3 1/2" or 5 1/4" size) containing the article. Identify clearly first author's name, file name, word processing program and version, and system (i.e. DOS or Mac). Clearly indicate the order and importance of headings.

• For detailed instructions regarding style and layout refer to *"Uniform requirements for manuscripts submitted to biomedical journals"*. Copies of this document may be obtained by writing to the Journal office, but the main points are summarized here. Articles should be submitted under conventional headings of *introduction, methods and materials, results, discussion,* but other headings will be considered if more suitable. Pages of text should be numbered consecutively.

• ***A title page*** should identify the title of the article which should be no more than 80 characters including spaces; name of institution(s) from which the work originated; and the name, address, telephone, and fax number of the corresponding author.

• ***Abstract*** Original Articles should be accompanied by an abstract of 250 words or less on a separate page, preferably in English and French, although the Journal will provide translation if required. Abstracts of original articles should consist of four paragraphs headed: *Background (or objective), Methods, Results and Conclusions.* Review articles should be accompanied by an abstract of 150 words or less.

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• The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

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Journals

Yang JF, Fung M, Edamura R, et al. H-Reflex modulation during walking in spastic paretic subjects. Can J Neurol Sci 1991; 18: 443-452.

Chapter in a book

McGeer PL, McGeer EG. Amino acid neurotransmitters. *In*: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. Basic Neurochemistry. Boston: Little, Brown & Co., 1981: 233-254.

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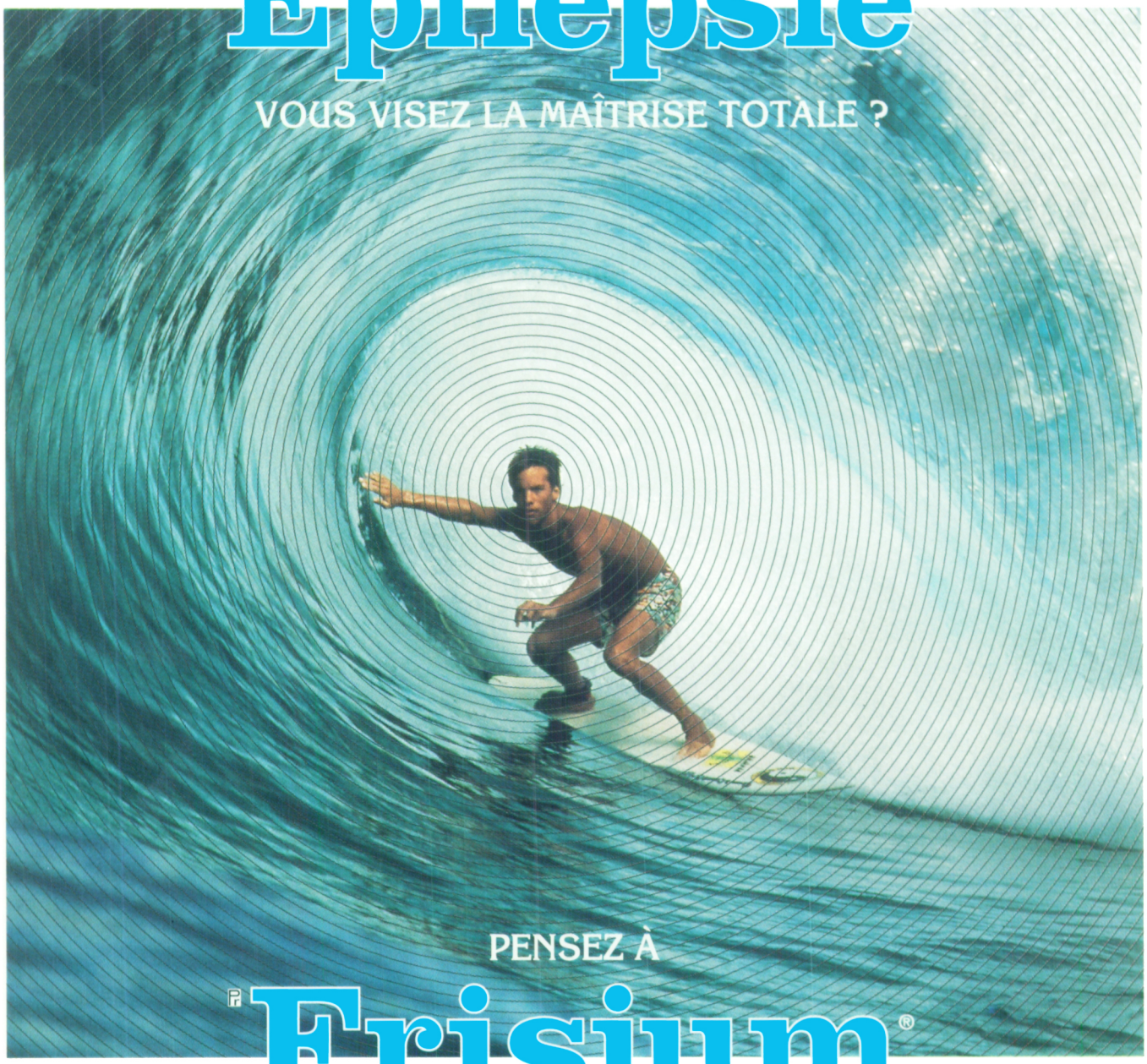

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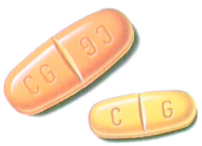

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