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of valproate and concomitant drug concentrations should be intensified whenever enzyme-inducing drugs are introduced or withdrawn.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 Dose (mg)**	**Dosage (mg) equivalent to valproic acid**		
kg	**lb**		**Dose 1**	**Dose 2**	**Dose 3**
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	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.

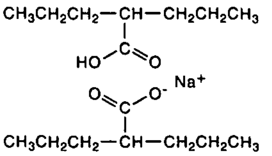
PHARMACEUTICAL INFORMATION:

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:* $C_{16}H_{31}NaO_4$

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.

REFERENCES: 1. Dean JC. Valproate. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practices.* Philadelphia, Pa: Lea & Febiger;1993:chap 77. 2. Wilder BJ, Ramsay RE, Murphy JV, Karas BJ, Marquardt K, Hammond EJ. Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology* 1983;33:1474-6. 3. Turnbull DM, Howel D, Rawlins MD, Chadwick DW. Which drug for the adult epileptic patient: phenytoin or valproate? *Br Med J* 1985;290:815-9. 4. Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. *Epilepsia* 1982;23:693-720. 5. Kakegawa N, Miyakoshi M, Seino M. Monopharmacy by sodium valproate (SV) and the blood concentration. In: Program and abstracts of the XI Epilepsy International Symposium; September 30, 1979; Firenze, Italy. Abstract:153. 6. Dreifuss FE, Langer DH. Side effects of valproate. *Am J Med* 1988;84 (suppl 1A):34-41. 7. Epival Product Monograph. Abbott Laboratories, Limited. 8. Manufacturers' Prescribing Information. 9. Wilder BJ, Rangel RJ. Review of valproate monotherapy in the treatment of generalized tonic-clonic seizures. *Am J Med* 1988;84(suppl 1A):7-13.

ABBOTT LABORATORIES, LIMITED
P.O. BOX 6150, STATION CENTRE-VILLE
MONTRÉAL, QUÉBEC H3C 3K6

Product Monograph available on request.

PAAB

See ifc.

Pr TEGRETOL®

Tablets
(Carbamazepine)
Suspension (100 mg/tsp)

THERAPEUTIC CLASSIFICATION

A. Anticonvulsant
B. For Symptomatic Relief of Trigeminal Neuralgia
C. 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, recourse to other accepted measures must be considered.

Carbamazepine is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

C. ***Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders:*** TEGRETOL may be used as mono-therapy or as an adjunct to lithium in the treatment of acute mania or prophylaxis of bipolar (manic-depressive) disorders in patients who are resistant to or are intolerant of conventional antimanic drugs. Carbamazepine may be a useful alternative to neuro-leptics 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.

These 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 (MAO) inhibitor. When it seems desirable to administer TEGRETOL to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of TEGRETOL should be low initially, and increased very gradually.

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

TEGRETOL should not be administered to patients with known hypersensitivity to carbamazepine, to any of the components of the tablets or suspension, or to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites, because of the similarity in chemical structure.

WARNINGS

ALTHOUGH REPORTED INFREQUENTLY, SERIOUS ADVERSE EFFECTS HAVE BEEN OBSERVED DURING THE USE OF TEGRETOL (CARBAMAZEPINE). AGRANULOCYTOSIS AND APLASTIC ANEMIA HAVE OCCURRED IN A FEW INSTANCES WITH A FATAL OUTCOME. LEUCOPENIA, THROMBOCYTOPENIA, HEPATOCELLULAR AND CHOLESTATIC JAUNDICE, AND HEPATITIS HAVE ALSO BEEN REPORTED. 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, TEGRETOL SHOULD BE WITHDRAWN AT ONCE.

LONG-TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK. THEREFORE, THE POSSIBLE RISK OF THE DRUG MUST BE WEIGHED AGAINST THE POTENTIAL BENEFITS BEFORE PRESCRIBING TEGRETOL TO INDIVIDUAL PATIENTS.

Pregnancy and Nursing

Women with epilepsy who are, or intend to become pregnant, should be treated with special care.

In women of childbearing potential, TEGRETOL should, whenever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with more than one anti-epileptic 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 from patients if required to prevent major seizures because of the risks posed, to both mother and fetus, by status epilepticus with attendant hypoxia.

The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk of malformations has been reported. There are rare reports on developmental disorders and malformations, including spina bifida, in association with carbamazepine. Conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

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 during the last weeks of pregnancy, as well as to the newborn, has been recommended.

Carbamazepine passes into breast milk in concentrations of about 25 - 60% of the plasma level. No reports are available on the long-term effect of breast feeding. The benefits of breast feeding should be weighed against the possible risks to the infant. Should the mother taking carbamazepine nurse her infant, the infant must be observed for possible adverse reactions, e.g., somnolence.

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

The reliability of oral contraceptives may be adversely affected by carbamazepine (see Drug Interactions section under Precautions).

PRECAUTIONS

Clinical Monitoring of Adverse Reactions: TEGRETOL (carbamazepine) should be prescribed only after a critical risk-benefit appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematological reactions to other drugs, or interrupted courses of therapy with TEGRETOL.

Careful clinical and laboratory supervision should be maintained throughout treatment. Should any signs or symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, TEGRETOL should be immediately discontinued until the case is carefully reassessed.

(a) ***Bone marrow function:*** Complete blood counts, including platelets and possibly reticulocytes and serum iron, should be carried out before treatment is instituted. Suggested guidelines for monitoring are weekly for the first month, then monthly for the next five months, thereafter 2 - 4 times a year. If low or decreased white blood cell or platelet counts are observed during treatment, the patient and the complete blood count should be monitored closely. Non-progressive fluctuating asymptomatic leucopenia, which is encountered, does not generally call for the withdrawal of TEGRETOL. However, treatment with TEGRETOL should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g., fever or sore throat, as this could indicate the onset of significant bone marrow depression.

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

(b) ***Hepatic function:*** Baseline and periodic evaluations of hepatic function must be performed, particularly in elderly patients and patients with a history of liver disease. 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 a continued course of treatment or following a decrease in dosage. However, the patient should be kept under close surveillance because of the rare possibility of Steven-Johnson syndrome or Lyell's syndrome occurring **(see WARNINGS)**.

Urinary Retention and Increased Intraocular Pressure: Because of its anticholinergic action, carbamazepine should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.

Occurrence of 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. Caution should also be exercised 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 heart 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, warn patients 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. Accordingly, patients should be advised to use some alternative, non-hormonal method of contraception.

Concomitant medication with TEGRETOL and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.

Carbamazepine may antagonize the effects of non-depolarising muscle relaxants (e.g., pancuronium); their dosage may need to be raised and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and its active 10,11-epoxide;

carbamazepine plasma levels should be monitored.

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

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

ADVERSE REACTIONS

The reactions which have been most frequently reported with TEGRETOL (carbamazepine) are CNS (e.g., drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions. These 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.

Rare: Elevated transaminases, jaundice, hepatitis of cholestatic, parenchymal (hepatocellular), or mixed type. Isolated cases: granulomatous hepatitis.

Dermatologic: Occasional or 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. Occasional: 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, collapse, 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: 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, taste disturbances.

Endocrine system and metabolism: Occasional: 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: gynecomastia, galactorrhea, 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: 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. Treatment should be discontinued 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 should be taken with meals whenever possible.

TEGRETOL Tablets, CHEWTABS and Suspension should be taken in 2 to 4 divided doses daily.

TEGRETOL Suspension should be well shaken before use since improper re-suspension may lead to administering an incorrect dose. Since a given dose of TEGRETOL Suspension produces higher peak carbamazepine levels than the same dose in tablet form, it is advisable to start with low doses and to increase slowly to avoid adverse reactions. When switching a patient from TEGRETOL Tablets to TEGRETOL Suspension, the same number of mg per day should be given in smaller, more frequent doses (i.e., BID Tablets to TID Suspension).

TEGRETOL CHEWTABS and the Suspension are particularly suitable for patients who have difficulty swallowing tablets or who need initial careful adjustment of dosage.

The controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid during or after a meal. These controlled release tablets should be prescribed as a twice-daily dosage. If necessary, three divided doses may be prescribed. 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 on the first day. Increase 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 anti-convulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except for phenytoin, which may be increased **(see Drug Interactions section under Precautions and Pregnancy And Nursing section under Warnings)**.

Use in Trigeminal Neuralgia: Initial daily dosage should be small; 200 mg taken in 2 doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg/day until relief of pain is obtained. This is usually achieved at dosage between 200-800 mg daily; but occasionally up to 1200 mg/day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimal effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of TEGRETOL at intervals of not more than 3 months, depending upon the individual clinical course.

Prophylactic use of the drug in trigeminal neuralgia is not recommended.

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.

AVAILABILITY OF DOSAGE FORM

	Pr TEGRETOL® Tablets 200 mg	Pr TEGRETOL® CHEWTABS 100 mg	Pr TEGRETOL® CHEWTABS 200 mg	Pr TEGRETOL® CR 200 mg	Pr TEGRETOL® CR 400 mg	Pr TEGRETOL® Suspension 100 mg/tsp
Colour	White	White with red specks	White with red specks	Beige-orange	Brown-orange	Orange
Shape	Round, flat-faced, bevel-edged	Round, flat-faced, bevel-edged	Oval, biconvex	Oval, slightly biconvex	Oval, slightly biconvex	
Imprint	Engraved GEIGY on one side and quadrisected 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 HC on the other. Bisected on both sides	CG/CG engraved on one side and ENE/ENE on the other. Bisected on both sides	Not applicable
Availability	Bottles of 100 & 500	Bottles of 100	Bottles of 100	Bottles of 100	Bottles of 100	Bottles of 450 mL
Storage Conditions	Store below 30°C, protect from humidity	Store below 30°C, protect from humidity and light	Store below 30°C, protect from humidity and light	Store below 25°C, protect from humidity	Store below 25°C, protect from humidity	Store below 30°C, protect from humidity and light

Tegretol is a schedule F drug and can only be obtained by prescription from a licensed practitioner. Product Monograph available on request. December 7, 1995

REFERENCES

1. Smith DB et al: Results of a nationwide veterans administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. Epilepsia 1987; 28(Suppl 3): 550-558.
2. Reynolds EH. Polytherapy, monotherapy, and carbamazepine. Epilepsia 1987; 28 (Suppl 3): 577-580.
3. Aldenkamp et al: Controlled release carbamazepine: cognitive side effects in patients with epilepsy. Epilepsia 1987; 28(Suppl 3): 507-514.
4. TEGRETOL® Product Monograph, November, 1995.

Geigy

Pharmaceuticals

Mississauga, Ontario L5N 2W5 or

Dorval, Quebec H9S 1B1

See obc, iii.

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

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

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

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

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 **For Information***

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

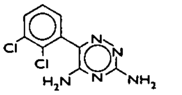
Geriatric Patients: There is little experience with the use of LAMICTAL in elderly patients. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions.

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.

References: 1. Goa KL *et al.* Lamotrigine: A review of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 1993;46(1):152-176. 2. Leach MJ *et al.* Neurochemical and behavioral aspects of lamotrigine. *Epilepsia* 1991;32(Suppl.2):S4-S8. 3. Data on file Glaxo Wellcome (GWMN[1]:6/95). 4. Brodie MJ. Lamotrigine versus other antiepileptic drugs: A star rating system is born. *Epilepsia* 1994;35(Suppl.5):S41-46. 5. Product Monograph of LAMICTAL, Nov. 1994. 6. Richens A, Yuen AWC. Overview of the clinical efficacy of lamotrigine. *Epilepsia* 1991;32(Suppl.2):S13-S16. 7. Betts T *et al.* Human safety of lamotrigine. *Epilepsia* 1991;32 (Suppl.2):S17-S21. 8. Binnie CD *et al.* Acute effects of lamotrigine (BW 430C) in persons with epilepsy. *Epilepsia* 1986;27(3):248-254. 9. Sander JWAS *et al.* A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy. *Epilepsy Res* 1990;6(3):221-226. 10. Yuen AWC. Lamotrigine: A review of antiepileptic efficacy. *Epilepsia* 1994;35(Suppl.5):S33-S36. 11. Binnie CD. Lamotrigine. *Comprehensive Epileptology*. New York Raven Press 1990:665-670. 12. Binnie CD *et al.* Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. *Epilepsy Res* 1989;4(3):222-229. 13. Dren AT *et al.* Placebo-controlled, dose-response evaluation of the efficacy and safety of lamotrigine (LAMICTAL) as add-on therapy in epileptic outpatients with partial seizures. *Epilepsia* 1991;32 (Suppl.3):20. 14. Gay PE *et al.* Chronic dose tolerance of lamotrigine and placebo in patients with epilepsy. *Epilepsia* 1988;29(5):686. 15. Jawad S *et al.* Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* 1989;30(3):356-363. 16. Loiseau P *et al.* A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures. *Epilepsy Res* 1990;7(2):136-145. 17. Matsuo F *et al.* Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. *Neurology* 1993;43:2284-2291. 18. Messenheimer J *et al.* Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. *Epilepsia* 1994;35(1):113-121. 19. Mikati MA *et al.* Long-term tolerability, pharmacokinetic and preliminary efficacy study of lamotrigine in patients with resistant partial seizures. *Clin Neuropharmacol* 1989;12(4):312-321. 20. Miller AA *et al.* Lamotrigine. *New Anticonvulsant Drugs* 1986; 165-177. 21. Risner ME *et al.* Multicenter, double-blind, placebo-controlled, add-on, crossover study of lamotrigine (Lamictal) in epileptic outpatients with partial seizures. *Epilepsia* 1990;31(5):619-620. 22. Schapel GJ *et al.* No effect of lamotrigine on carbamazepine and carbamazepine-epoxide concentrations. *Epilepsia* 1991;32 (Suppl.1):58. 23. Smith D *et al.* Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia* 1993;34(2):312-322. 24. Betts T. Clinical use of lamotrigine. *Seizure* 1992;1:3-6. 25. Binnie CD. The efficacy of lamotrigine. *Rev Contemp Pharmacother* 1994;5:115-122. 26. Cohen AF *et al.* Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. *Br J Clin Pharmacol* 1985;20:619-629.

GlaxoWellcome
Glaxo Wellcome Inc.
Mississauga, Ontario, Canada L5N 6L4
90995 LAM PAAB CCPP

Table 2: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Add-On Trials (Events in a 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	400 mg
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	Dose Regimen (mg)
>60	1200 mg	400 Three times a day
30-60	600 mg	300 Twice a day
15-30	300 mg	300 Once a Day
<15	150 mg	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.

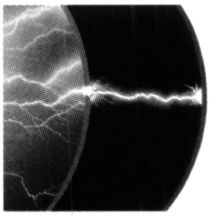
Composition

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.

Product Monograph available upon request.



NEURONTIN*

(gabapentin capsules)

Easy to add-on

PARKE-DAVIS

Scarborough, Ontario M1L 2N3

*T.M. Warner-Lambert Company, Parke-Davis Division, Warner-Lambert Canada Inc., auth. user.

PMAC PAAB CCPP

See pages ix, xv.

℞ IMITREX®

(sumatriptan succinate)

50 and 100 mg Tablet

6 mg Subcutaneous Injection and Autoinjector

THERAPEUTIC CLASSIFICATION: Migraine Therapy

PHARMACOLOGIC CLASSIFICATION: 5-HT$_1$ Receptor Agonist

CLINICAL PHARMACOLOGY

IMITREX (sumatriptan succinate) is a selective 5-hydroxytryptamine1 (5-HT$_1$) receptor agonist which has been shown to be effective in relieving migraine headache. The activity of sumatriptan at the 5-HT$_1$ 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$_1$ 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$_1$ 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 known 5-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 ischemic 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, and in patients receiving treatment with monoamine oxidase inhibitors or use within two weeks of discontinuation of MAOI therapy. Until further data are available the use of sumatriptan is contraindicated in patients with hemiplegic migraine, basilar migraine and in patients receiving treatment with 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 should only be used where there is a clear diagnosis of migraine headache. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. There have been rare reports where patients received sumatriptan for severe headaches which subsequently were shown to have been secondary to an evolving neurological lesion (cerebrovascular accident, subarachnoid haemorrhage). In this regard, it should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischemic attack). However, if a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given.

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 arrhythmia, ischemia or myocardial infarction. Serious coronary events following sumatriptan have occurred but are extremely rare. Although it is not clear how many *of these can be attributed to sumatriptan, because of its potential to cause coronary* vasospasm, sumatriptan should not be given to patients in whom unrecognized coronary artery disease (CAD) is likely without a prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over 40, patients with risk factors for CAD (hypertension, hypercholesterolaemia, obesity, diabetes, smoking, or strong family history of CAD). 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. 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 ischemic 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 ischemic 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 ischemic ST wave elevations associated with IMITREX injection.

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. Sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions which lower their convulsion threshold. Chest, jaw or neck tightness is relatively common (3-5% in controlled clinical trials) after IMITREX injection, but has only been rarely associated with ischemic 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 e.g. driving or operating machinery if drowsiness occurs.

Concomitant Disease: Since there have been rare reports of seizures occurring, sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions which lower their convulsive threshold.

Concomitant Medications: There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of *sumatriptan. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.*

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

Hepatic Impairment: The effect of hepatic impairment on the efficacy and safety of sumatriptan has not been evaluated, however, the pharmacokinetic profile of sumatriptan in patients with moderate[1] hepatic impairment shows that these patients, following an oral dose of 50 mg, have much higher plasma sumatriptan concentrations than healthy subjects. Therefore, an oral dose of 50 mg may be considered in patients with hepatic impairment.

[1]Assessed by aminopyrine breath test (>0.2-0.4 scaling units).

Pharmacokinetic Parameters After Oral Administration of Sumatriptan 50 mg to Healthy Volunteers and Moderately Hepatically Impaired Patients

Parameter	Mean Ratio (hepatic impaired/healthy) n=8	90% CI	p-value
AUC_∞	181%	130 to 252%	0.009*
Cmax	176%	129 to 240%	0.007*

* Statistically significant

The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects.

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 foetuses. 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.

In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 150 times those seen in humans after a 6 mg subcutaneous dose and approximately 200 times those seen in humans after a 100 mg oral dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 100 times those in humans by the subcutaneous route and approximately 150 times those in humans by the oral route.

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 propranolol, 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. Hypotension, bradycardia, tachycardia and palpitations have been reported rarely. 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 ischemic ST elevation associated with IMITREX injection (see WARNINGS). 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. Hypersensitivity reactions to sumatriptan have been reported including anaphylactic shock, anaphylactoid reactions, rash, urticaria, pruritis and erythema. There have been rare reports of seizures, the majority of these patients have a previous history of epilepsy or structural lesions predisposing to epilepsy (see PRECAUTIONS).

The following 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.

Incidence of 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%

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 are as follows: One patient received two 6 mg subcutaneous doses within 30 minutes and 1 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. 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.

However, based on the physician's clinical judgement, a 50 mg dose may be considered adequate. The appropriateness should be based on the patient's needs and response to treatment.

Patients who have had a successful response (i.e. no pain or mild pain) may treat a later recurrence of headache with an additional 100 mg dose of sumatriptan. Not more than 300 mg should be taken in any 24 hour period.

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.

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.

Hepatic Impairment: A 50 mg dose (single tablet) may be considered for patients with hepatic impairment, since plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed in patients with mild or moderate impairment following a 50 mg oral dose (see Precautions).

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 (i.e. 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.

For IMITREX injection, it is recommended to start the treatment at the first sign of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. The efficacy of sumatriptan is independent of the duration of the attack when starting treatment. Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.

Patients should be advised to read the patient instruction leaflet regarding the safe disposal of syringes and needles.

STABILITY AND STORAGE RECOMMENDATIONS IMITREX Tablets should be stored at 2°C to 30°C. IMITREX Injection should be stored between 2°C to 30°C and protected from light.

COMPOSITION IMITREX TABLETS contain 100 mg or 50 mg sumatriptan (base) as the succinate salt. Imitrex Tablets also contain lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

IMITREX INJECTION contains 6 mg sumatriptan (base) as the succinate salt in an isotonic sodium chloride solution.

AVAILABILITY OF DOSAGE FORMS IMITREX (sumatriptan succinate) TABLETS 100 mg are pink film-coated tablets available in blister packs containing 6 tablets, packed in a cardboard carton.

Imitrex (sumatriptan succinate) TABLETS 50 mg are white film-coated tablets available in blister packs containing 6 tablets.

Each tablet contains 100 mg or 50 mg sumatriptan (base) as the succinate salt.

IMITREX INJECTION is available in pre-filled 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 pre-filled syringes plus an autoinjector are packed in a patient starter kit. A refill pack is available containing 2 x 2 pre-filled 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 Wellcome 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 Wellcome Inc., 1994.

℞ IMITREX®

SUMATRIPTAN SUCCINATE

See pages vi, vii.

See ibc, xvi.

The Division of Neurology at the University of Alberta has opportunities for neurologists looking for a career in academic neurology with the following qualifications:

1. The candidate must have passed the Royal College fellowship examination in Neurology or the examinations of the American Board of Psychiatry and Neurology (Neurology).
2. The candidate must have completed a fellowship in an academic institution following residency.
3. Teaching and research experience beyond fellowship is desirable.
4. The candidate must have a commitment to academic neurology as evidenced by scholarly publications or proficiency in an area of clinical or basic research.
5. Preference will be given to candidates with interests in the area of Stroke, Epilepsy or Neurodegenerative diseases, particularly Alzheimer's or related disorders.

The position will be 75% research and 25% clinical with guaranteed protected time for academic activities. The appointment will be a full-time tenure track appointment. The rank and salary will be commensurate with the candidate's experience, from Assistant Professor to Full Professor.

The Division of Neurology is a part of the Department of Medicine. The University provides an active and stimulating academic environment with excellent basic science facilities. We provide services for Edmonton and Northern Alberta and surrounding provinces with a patient population of over 1 million. Areas of active research include stroke, neuromuscular disease, multiple sclerosis and movement disorders.

In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Interested applicants are asked to forward their CV and the names and addresses of three references, by September 15, 1996, to:

Dr. Michael H. Brooke
Director, Division of Neurology
University of Alberta School of Medicine
Room 2E3.12, Mackenzie Health Sciences Centre
Edmonton, Alberta, Canada T6G 2B1

The University of Alberta is committed to the principle of equity in employment. As an employer we welcome diversity in the workplace and encourage applications from all qualified women and men, including Aboriginal peoples, persons with disabilities, and members of visible minorities.

THE ANNE AND MAX TANENBAUM CHAIRS PROGRAM IN BIOMEDICAL RESEARCH AT THE UNIVERSITY OF TORONTO

Funded by an endowment from Anne Tanenbaum, a Joint Chair program in biomedical research has been established by the University of Toronto, in cooperation with Baycrest Centre for Geriatric Care, the Hospital for Sick Children, Mount Sinai Hospital, and The Toronto Hospital to honour Anne and Max Tanenbaum. The purpose of the Joint Chair program is to support research priorities in Molecular Medicine or in Neuroscience at each of the five institutions by providing each institution with funding for an endowed Chair. The Chair is to be awarded to an outstanding researcher who has clearly established an international leadership in an area of research identified as a priority by the institution in either Molecular Medicine or in Neuroscience.

The Rotman Research Institute of Baycrest Centre has as its research focus **COGNITIVE NEUROSCIENCE**. The emphasis on the Baycrest Chair is particularly on the application of electrophysiological procedures to understand cognitive functioning. The successful applicant should be an independent researcher with an international reputation in cognitive electrophysiology, and the use of event-related potentials to study normal aging, and effects of neurological disorders. The successful applicant will have a fully equipped ERP lab, computer programmer, and scientists who will be hired in the same area.

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

Applicants should submit, along with a covering letter describing current research interests, and future research goals, a C.V., relevant reprints and have three letters of reference sent independently by September 27, 1996 to:

Dr. Donald T. Stuss
Director, Rotman Research Institute
Baycrest Centre for Geriatric Care
3560 Bathurst Street, Toronto, Ontario,
CANADA M6A 2E1
Tel: (416) 785-2500 x 2522
Fax: (416) 785-2862
Email: stuss@psych.toronto.edu

ADVERTISERS INDEX

Abbott
Epival – ifc, xvii, xviii

Berlex
Betaseron – xi, xxi, xxii

Ciba Geigy
Tegretol – obc, iii, xix, xx

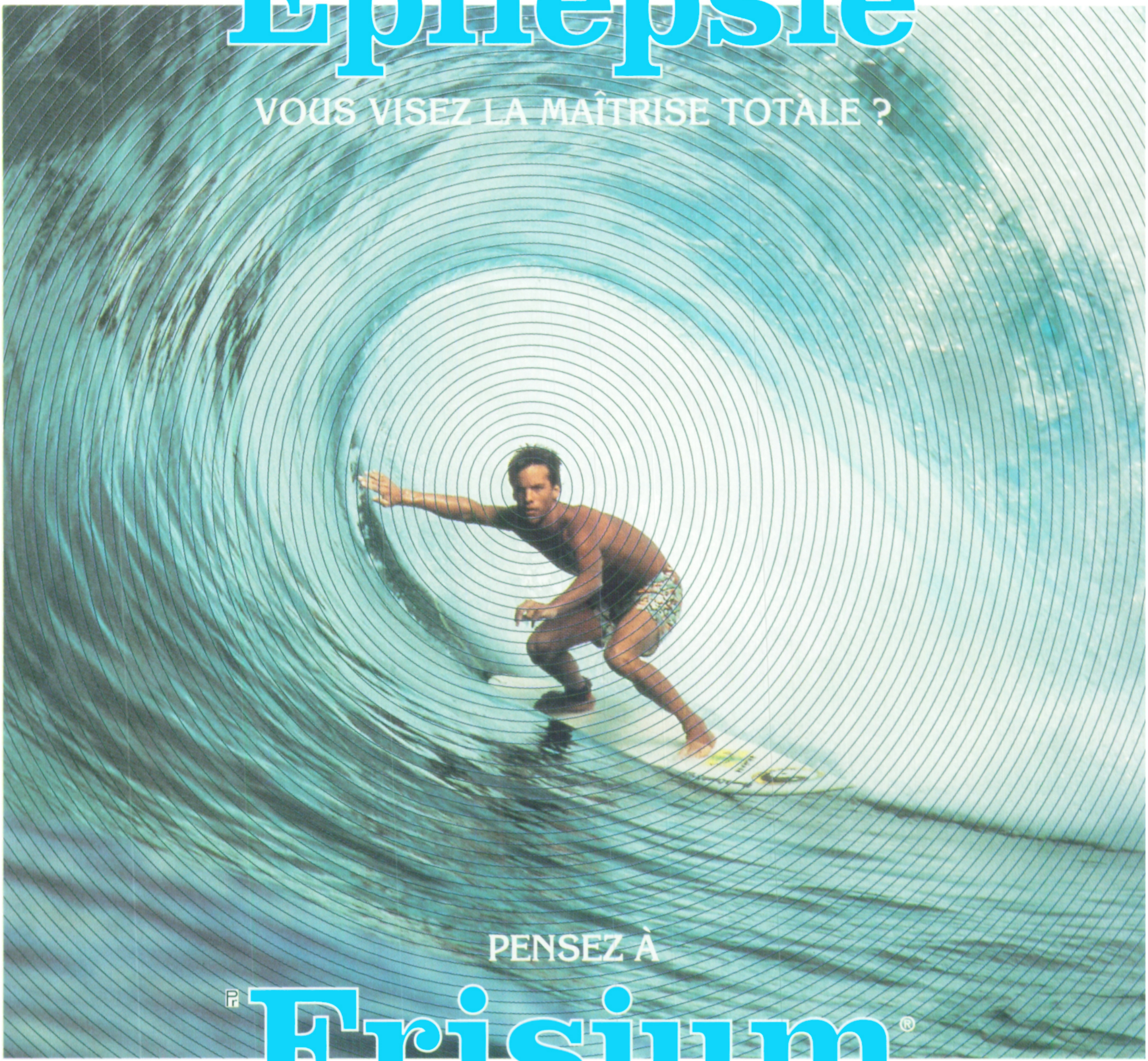
Glaxo Wellcome
Imitrex – vi, vii, xxvii
Lamictal – iv, v, xii, xiii, xxiii, xxiv

Hoechst Marion Roussel
Frisium – ibc, xvi, xxviii

King Medical – xxix

Parke Davis
Neurontin – ix, xv, xxv, xxvi

Classified Ads
– xxix



(clobazam)

- Maîtrise totale des crises chez un pourcentage impressionnant de patients[1].
- Frisium est «un antiépileptique remarquablement efficace et [généralement] sûr lorsqu'il est ajouté au traitement»[1].
- Frisium est efficace contre *tous* les types de crises de l'enfant *et* de l'adulte[2].
- La posologie est d'une dose par jour, à prendre de préférence au coucher.*

Pour une approche globale de la maîtrise des crises

*La dose quotidienne peut être fractionnée chez certains patients.

Frisium est indiqué pour le traitement adjuvant des épileptiques lorsqu'un traitement anticonvulsivant habituel ne suffit pas à stabiliser. Comme avec toutes les benzodiazépines, les patients, surtout les personnes âgées, doivent donc en être prévenus. Les effets indésirables les plus fréquents (> 1 %) sont l'ataxie, le gain de poids, les étourdissements et la nervosité.

Hoechst-Roussel Canada Inc.
Montréal, Québec H4R 2E8

CCPP AD-FRI-01/95F

Pour documentation voir pages xxviii.

Tegretol®
(carbamazepine) is
NOW
also available
as **Suspension**

Tegretol®
carbamazepine

Please see prescribing information on all dosage forms.

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

Excellent Seizure Control.

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

Consistent Blood Levels.

Tegretol CR delivers fewer "peaks and valleys" in blood levels than conventional Tegretol. That means fewer side effects and a more stable pattern of cognitive functioning.[3]

The most commonly reported side effect with carbamazepine is drowsiness. This reaction usually occurs only during the initial phase of therapy[4] and can be minimized by using controlled-release carbamazepine (TEGRETOL®CR).[3]

Convenient B.I.D. Dosing.

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

TEGRETOL® CR.

Helping epilepsy patients reach their full potential.

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

PMAC ACIM PAAB CCPP G-95111E

For brief prescribing information see pages xix, xx.