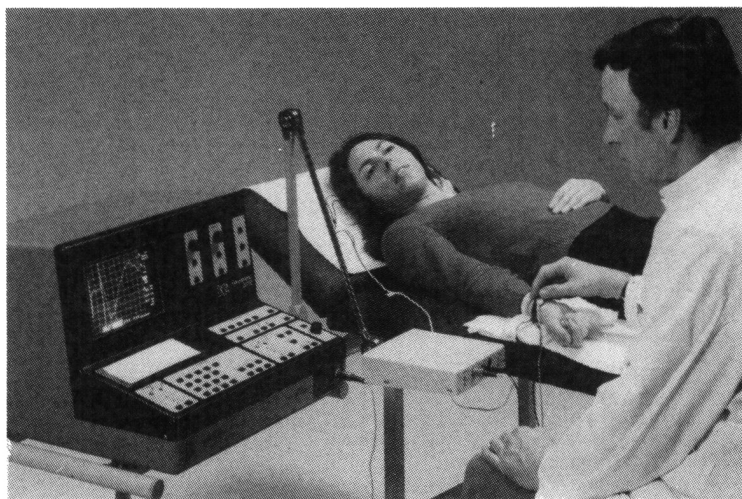
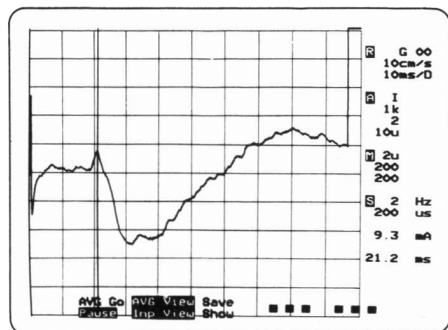


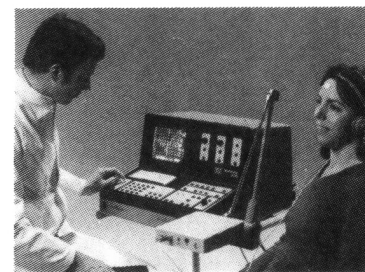
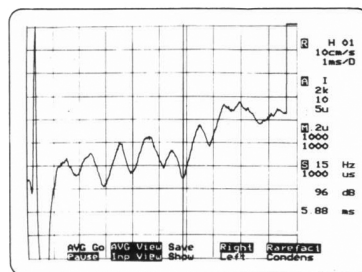
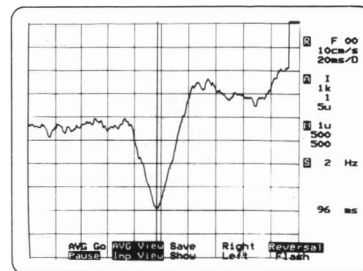
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Tegretol® 200 mg (carbamazepine) tablets

Tegretol® Chewtabs™ (carbamazepine chewable tablets) 100 mg

For Symptomatic Relief of Trigeminal Neuralgia Anticonvulsant

Action: TEGRETOL (carbamazepine) has anticonvulsant properties which have been found useful in the treatment of psychomotor and other partial epilepsies, when administered in conjunction with other anticonvulsant drugs to prevent the possible generalization of the epileptic discharge. A mild psychotropic effect has been observed in some patients, which seems related to the effect of the carbamazepine in psychomotor or temporal lobe epilepsy. TEGRETOL relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours.

Indications and Clinical Use

A. Trigeminal Neuralgia: For the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). Do not use 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. TEGRETOL is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

B. TEGRETOL has been found useful:

- 1) in the management of psychomotor (temporal lobe) epilepsy, and,
- 2) as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication.
- 3) as an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs.

TEGRETOL is ineffective in controlling petit mal, minor moto. myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge.

Warnings

Although reported infrequently, serious adverse effects have been observed during the use of TEGRETOL. Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia and hepatocellular and cholestatic jaundice have also been reported. It is, therefore, important that TEGRETOL should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia. Long-term toxicity studies in rats indicated a potential carcinogenic risk. Therefore, the possible risk of drug use must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

Contraindications

Hepatic disease, serious blood disorder, less than 14 days either before or after monoamine oxidase inhibitor (then the dosage of TEGRETOL should be low initially, and increased very gradually), atrioventricular heart block, hypersensitivity to tricyclic compounds, lactation, first trimester of pregnancy.

Usage in Pregnancy

As safety has not been established, TEGRETOL should not be given to women of childbearing potential unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the foetus.

Precautions

Monitoring of Haematological and Other Adverse Reactions: Complete blood studies, including platelet counts, and evaluation of hepatic and renal function and urinalysis should be carried out before treatment is instituted and frequent clinical and laboratory supervision should be maintained throughout treatment. If any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, TEGRETOL should be immediately discontinued.

Urinary Retention and Increased Intraocular Pressure: Caution is advised in patients with increased intraocular pressure or urinary retention due to the drug's anticholinergic action.

Occurrence of Behavioural Disorders:

TEGRETOL may activate a latent psychosis, or, in elderly patients, produce agitation or confusion. Caution is advised in alcoholics.

Use in Patients with Cardiovascular Disorders:

Caution is advised in patients with a history of coronary artery disease, organic heart disease, or congestive failure. An E.K.G. should be performed if a defective conductive system is suspected before administering TEGRETOL, in order to exclude patients with atrioventricular block.

Use in Patients taking Oral Contraceptives:

Women under treatment with TEGRETOL and oral contraceptives, should be advised to use some alternative, non-hormonal method of contraception as the reliability of oral contraceptives may be adversely affected.

Driving and Operating Hazardous Machinery:

Warn patients about the possible hazards of operating machinery or driving automobiles as dizziness and drowsiness are possible side effects of TEGRETOL.

Adverse Reactions

Haematological reactions: Transitory leucopenia, eosinophilia, leucocytosis, thrombocytopenic purpura, agranulo-

cytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.

Hepatic Disturbances: Abnormalities in liver function tests, cholestatic or hepatocellular jaundice.

Dermatological Reactions: Skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus erythematosus.

Neurological Reactions: Vertigo, dizziness, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, increase in motor seizures, peripheral neuritis, paresthesia, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency.

Cardiovascular Systems: Recurrence of thrombophlebitis, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.

Genitourinary Reactions: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, impotence, elevation of BUN, albuminuria, and glycosuria.

Digestive Tract: Nausea, vomiting, gastric or abdominal discomfort, diarrhoea, anorexia, dryness of the mouth and throat, glossitis and stomatitis.

Eyes: There is no conclusive evidence that TEGRETOL produces pathological changes in the cornea, lens or retina. However, it should be recognized that many phenothiazines and related drugs have been shown to cause eye changes. By any type, periodic eye examinations, including slitlamp funduscscopy and tonometry, are recommended.

Other Reactions: Fever and chills, lymphadenopathy, aching joints and muscles, leg cramps and conjunctivitis.

Symptoms and Treatment of Overdosage

Symptoms: Dizziness, ataxia, drowsiness, stupor, nausea, vomiting, restlessness, agitation, disorientation; tremor, involuntary movements, opisthotonos, abnormal reflexes (slowed or hyperactive); mydriasis, nystagmus; flushing, cyanosis, urinary retention, hypotension, hypertension, coma. The EEG may show dysrhythmias. The laboratory findings have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria.

Treatment: No known specific antidote. Induce emesis. Perform gastric lavage. Watch vital signs and administer symptomatic treatment as required. Hyperirritability may be controlled by the administration of parenteral barbiturates. Barbiturates should not be used if monoamine oxidase inhibitors have also been taken by the patient, either in overdosage or in recent therapy (within two weeks). Barbiturates may induce respiratory depression, particularly in children, therefore, have equipment available for artificial ventilation and resuscitation. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression. Treat shock (circulatory collapse) with supportive measures, including intravenous fluids, oxygen, and corticosteroids. Electrocardiogram should be monitored, particularly in children, to detect any cardiac arrhythmias or conduction defects.

Dosage and Administration

Use in Epilepsy (see Indications): A low initial daily dosage with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient. **Adults and Children over 12 years of age:** Initially: 100 to 200 mg once or twice a day. The initial dosage is progressively increased, until the best response is obtained, up to 600 mg daily. Usual Daily Dosage: 600 mg, however up to 800 to 1000 mg have been used for short periods. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

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

Use in trigeminal neuralgia: Initial daily dosage: 100 mg twice daily may be increased by 200 mg per day until relief of pain is obtained. Usual dosage: 200 to 800 mg daily. Up to 1200 mg daily may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimum 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 in trigeminal neuralgia is not recommended. Administer in two or three divided doses daily, with meals whenever possible.

Dosage Forms

TEGRETOL® tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. TEGRETOL® Chewtabs™ 100 mg: Pale pink, round, flat, bevel-edged tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each chewable tablet contains 100 mg carbamazepine.

Availability

TEGRETOL® tablets 200 mg: Bottles of 100 and 500 tablets. Protect from heat and humidity. TEGRETOL® Chewtabs™ 100 mg: Bottles of 100. Protect from heat and humidity.

Full information available on request.

References

- 1 Troupin, A.S.: The Choice of Anticonvulsants, Proceedings of the 25th Western Institute on Epilepsy, March 26, 1975, Las Vegas, Nevada.
- 2 Antiepileptic Drugs, Second Edition, Woodbury, Penry, Pippenger, Raven Press, p. 513.
- 3 Thompson, P.J. and Trimble, M.R.: Anticonvulsant Drugs and Cognitive Functions, Epilepsia, 23: 531-544, 1982.

Geigy

Mississauga, Ontario L5N 2W5

(see pages vi & vii)

Lioresal® (baclofen)

Muscle relaxant Antispastic agent

Indications and Clinical Uses

Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Spinal cord injuries and other spinal cord diseases.

Contraindications

Hypersensitivity to LIORESAL.

Warnings

Abrupt Drug Withdrawal: Except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued to prevent visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, insomnia, and worsening of spasticity. **Impaired Renal Function:** Caution is advised in these patients and reduction in dosage may be necessary. **Stroke:** Has not been of benefit and patients have shown poor tolerability to the drug.

Pregnancy and Lactation: Not recommended as safety has not been established. High doses in rats and rabbits are associated with an increase of abdominal hernias and ossification defects in the fetuses.

Precautions

Not recommended in children under 12 as safety has not been established. Because sedation may occur, caution patients regarding the operation of automobiles or dangerous machinery, activities made hazardous by decreased alertness, and use of alcohol and other CNS depressants. Use with caution in spasticity that is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function, epilepsy or history of convulsive disorders (clinical state and EEG should be monitored), peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and patients receiving antihypertensive therapy.

Adverse Reactions

Most common adverse reactions are transient drowsiness, dizziness, weakness and fatigue. Others reported:

Neuropsychiatric: Headache, insomnia, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizures. **Cardiovascular:** Hypotension, dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea, constipation, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool. **Genitourinary:** Urinary frequency, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion. Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

The following laboratory tests have been found to be abnormal in a few patients receiving LIORESAL: SGOT, alkaline phosphatase and blood sugar (all elevated).

Symptoms and Treatment of Overdosage

Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures. Co-administration of alcohol, diazepam, tricyclic anti-depressants, etc., may aggravate the symptoms.

Treatment: Treatment is symptomatic. In the alert patient, empty the stomach (induce emesis followed by a cuffed endotracheal tube before beginning lavage (do not induce emesis).

Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. Maintain high urinary output. Dialysis is indicated in severe poisoning associated with renal failure.

Dosage and Administration

Optimal dosage of LIORESAL requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually 40-80 mg daily).

The following dosage titration schedule is suggested:
5 mg t.i.d. for 3 days 15 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days 20 mg t.i.d. for 3 days
Total daily dose should not exceed a maximum of 20 mg q.i.d.

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).

Availability

LIORESAL (baclofen) 10 mg tablets. White to off-white flat-faced, oval tablets with GEIGY monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side.

Available in bottles of 100 tablets. Product Monograph supplied on request.

References:

- 1 Feldman et al, Neurology, Vol. 28, No. 11 pp 1094-1098, 1978.
2. Symposia Reporter, Vol. 3, No. 2.

G-3017

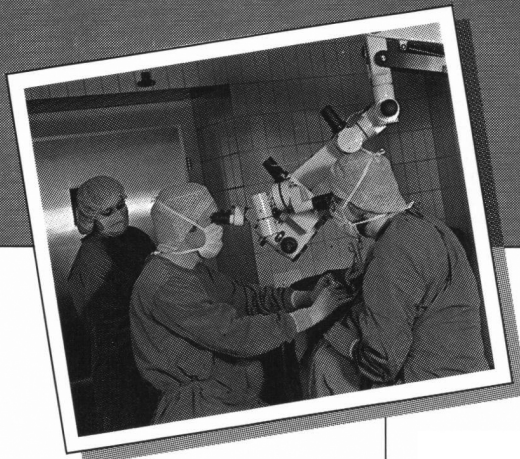
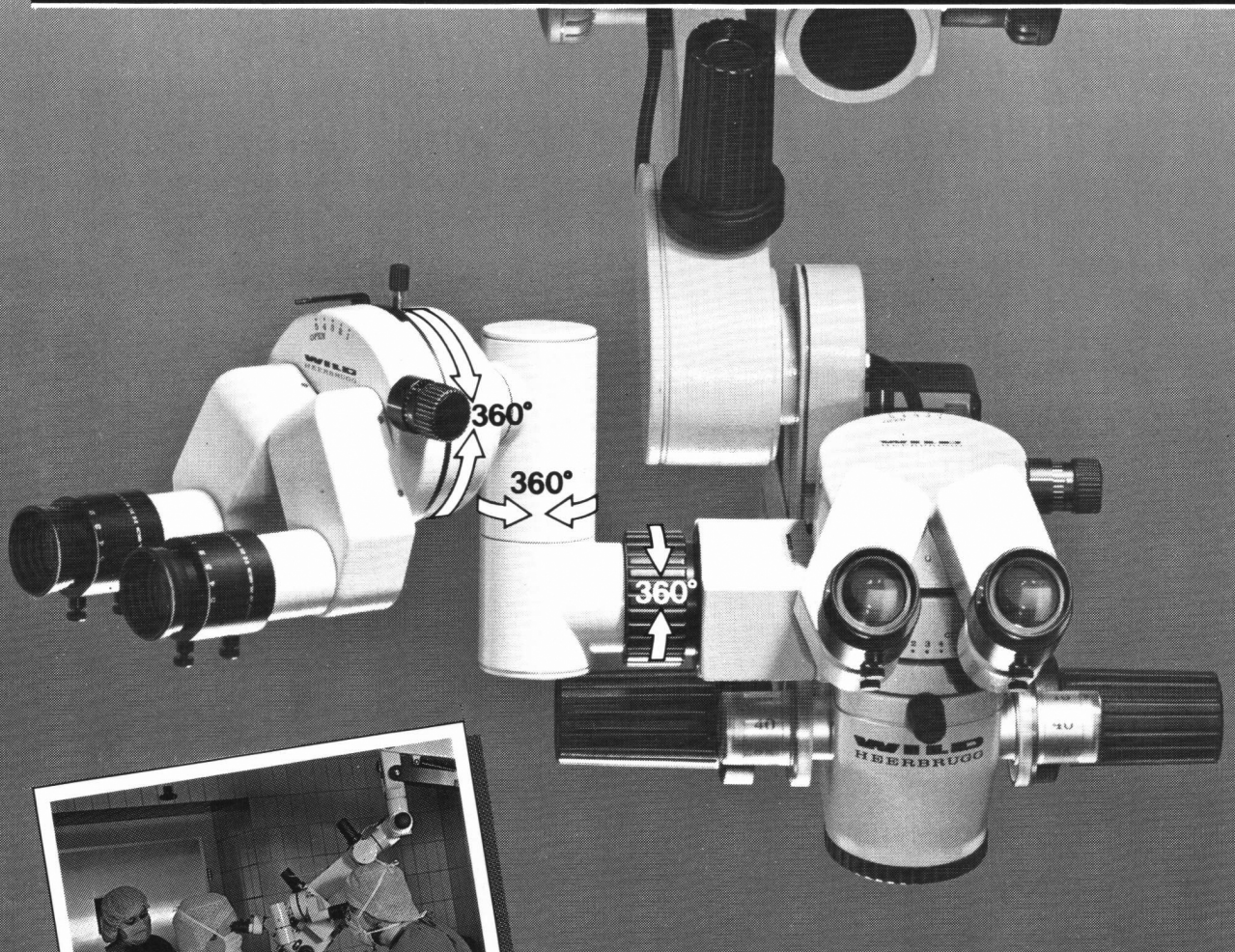
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Neurosurgeon

The Moncton Hospital, a teaching 540-bed Regional Hospital, is looking for an additional Neurosurgeon to join two active staff Neurosurgeons.

The Hospital, currently undergoing a \$50 million redevelopment project, serves as the Neurological and Trauma Centre to a population base of over 500,000 people.

Candidates should be eligible for licensure in the Province of New Brunswick and be certified with the Royal College of Physicians and Surgeons of Canada.

Applications may be submitted in confidence to:

Dr. Ginette Gagné-Koch
Medical Director
The Moncton Hospital
135 MacBeath Avenue
Moncton, N.B.
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Neurosurgeon

Required for a progressive regional municipality, population 158,000, situated in a mid-northern university city. Excellent facilities in all fields of recreation, arts and education. The city has three general hospitals with a broad range of medical specialities.

Support services include a CT scan, nuclear medicine, and an EEG department. There are two neurosurgeons on staff. Unlimited scope for private practice. Applicants must have LMCC and Fellowship.

Please address inquiries to:

Dr. R. Grosso, Chief of Staff
Sudbury General Hospital
of The Immaculate Heart of Mary
700 Paris Street
Sudbury, Ontario P3E 3B5
Telephone: 674-3181, Ext. 179

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Please submit curriculum vitae and three references to:

J. Gregory Cairncross, M.D.
The London Regional Cancer Centre
391 South Street
London, Ontario, Canada
N6A 4G5

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Enteric-coated
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divalproex sodium

**Now indicated for generalized seizures
with tonic-clonic manifestations**



Epival, an anticonvulsant recognized in the treatment of absence, has now been approved for primary generalized seizures with tonic-clonic manifestations. This broad spectrum of indications means that Epival can be used solely or adjunctively to help more of your epileptic patients with multiple seizure types which include either absence or tonic-clonic seizures.

Epival is available in enteric-coated tablets that help reduce the risk of poor compliance caused by gastric irritation.¹ Three strengths are available, including a 125-mg tablet that is small enough for children to swallow easily.

in absence or tonic-clonic seizures

Epival
divalproex sodium

a better life for more epileptic patients

1. Wilder BJ et al.
Clin Pharmacol Ther
1983; (34):4501-504.

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ACTION: 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 of 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 anti-epileptic drugs. 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 dose may result in decreases in the extent of protein binding and variable changes in valproic acid clearance and elimination. The therapeutic plasma concentration range is believed to be from 50 to 100 $\mu\text{g/mL}$. 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.

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. See "Metabolism" subsection regarding statement on other metabolites in the urine.

See WARNINGS section regarding statement on fatal hepatic dysfunction.

INDICATIONS AND CLINICAL USE: 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.

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

CONTRAINDICATIONS: 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. These incidences usually have occurred during the first 6 months of treatment with valproic acid. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed 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 decrease in concentrations 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. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of 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 "Reproductive Studies" in section on 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 anti-epileptic 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 eg, congenital malformations of the heart, cleft lip and/or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

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

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

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

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

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

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK (See section on TOXICOLOGY).

PRECAUTIONS: Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

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

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

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

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

Driving and Hazardous Occupations: 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.

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

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

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

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

Caution is recommended when divalproex sodium is ad-

ministered with drugs affecting coagulation, eg, acetylsalicylic acid and warfarin (See ADVERSE REACTIONS).

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

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

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

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

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

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

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

Musculoskeletal: Weakness has been reported.

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

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

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

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

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 anti-epileptic effects of Epival, it should be used with caution.

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.

DOSE AND ADMINISTRATION: 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 exceeds 125 mg, it should be given in a divided regimen (See Table).

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

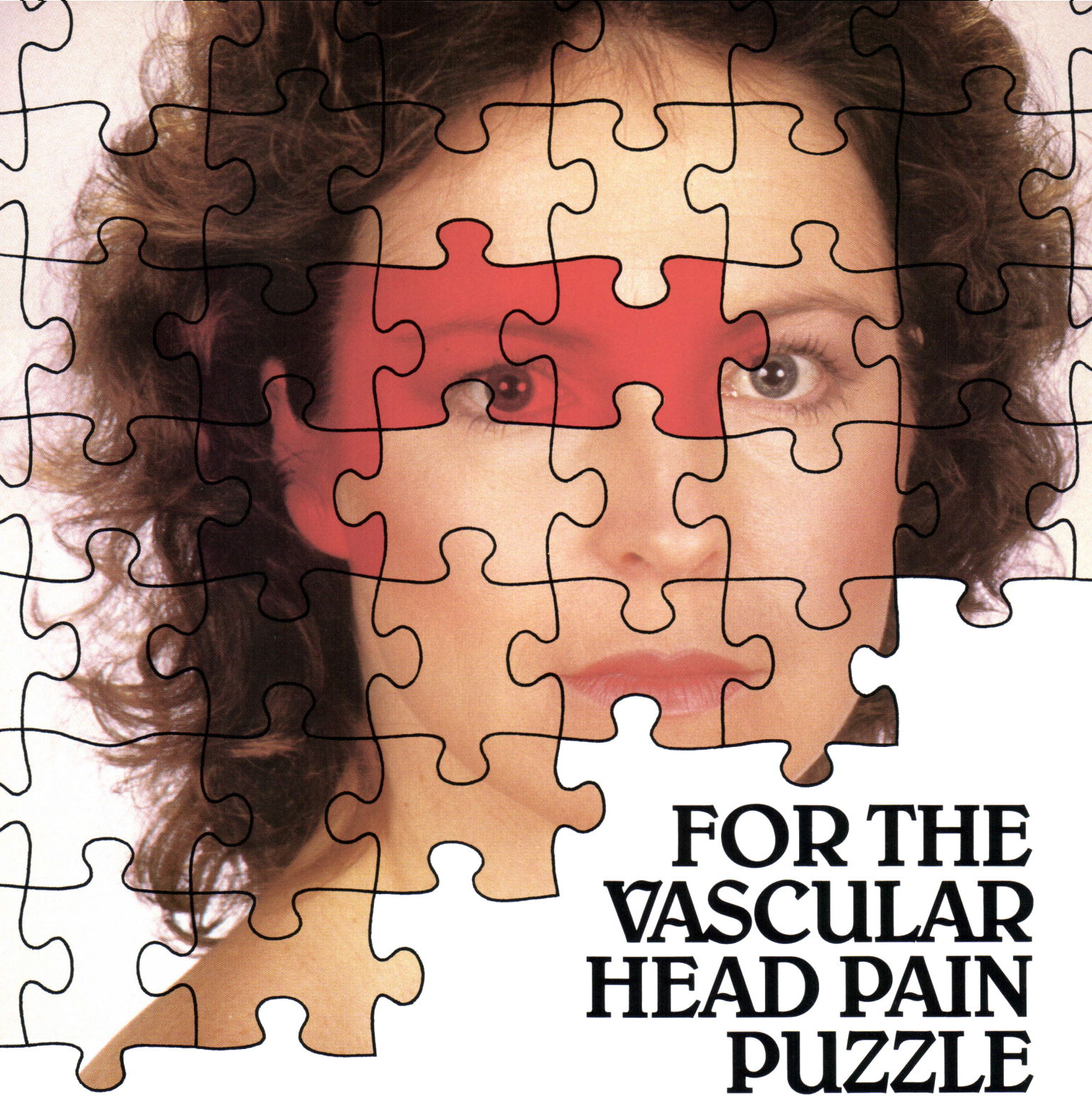
Table of Initial Doses by Weight (based on 15 mg/kg/day)

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

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

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

AVAILABILITY: Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink colored tablets of 125 mg, peach-colored tablets of 250 mg, lavender-colored tablets of 500 mg. Supplied in bottles of 100 tablets.



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For brief prescribing information see page xii

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