Brief Prescribing Information

Ⓡ Tegretol® *(carbamazepine)*

TEGRETOL® 200 mg
TEGRETOL® CHEWTABS™ 100 mg and 200 mg
TEGRETOL® CR 200 mg and 400 mg

Action

TEGRETOL (carbamazepine) has anticonvulsant properties which have been found useful in the treatment of psychomotor epilepsy and, as an adjunct in the treatment of partial epilepsies, when administered in conjunction with other anticonvulsant drugs to prevent the possible generalization of the epileptic discharge. A mild psychotropic effect has been observed in some patients, which seems related to the effect of the carbamazepine in psychomotor or temporal lobe epilepsy.

TEGRETOL relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours.

Like other tricyclic compounds, TEGRETOL has a moderate anticholinergic action which is responsible for some of its side effects. A tolerance may develop to the action of TEGRETOL after a few months of treatment and should be watched for.

TEGRETOL may suppress ventricular automaticity due to its membrane-depressant effect similar to that of quinidine and procainamide, associated with suppression of phase 4 depolarization of the heart muscle fibre. A number of investigators have reported a deterioration of EEG abnormalities with regard to focal alterations and a higher incidence of records with nil beta activity, during carbamazepine-combined treatment.

The absorption of carbamazepine in man is relatively slow. When taken in a single oral dose, TEGRETOL (carbamazepine tablets) and TEGRETOL CHEWTABS (carbamazepine chewable tablets) yield peak plasma concentrations of unchanged carbamazepine within 4-24 hours. With respect to the quantity of carbamazepine absorbed, there is no clinically relevant difference between the various dosage forms. When TEGRETOL CR (carbamazepine controlled release tablets) are administered repeatedly, they yield a lower average maximal concentration of carbamazepine in the plasma, without a reduction in the average minimal concentration. This tends to result in a lower incidence of intermittent concentration-dependent adverse drug reactions. It also ensures that the plasma concentrations remain largely stable throughout the day, thereby making it possible to manage with a twice-daily dosage.

Carbamazepine becomes bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in the saliva reflects the non-protein-bound portion present in the serum (20-30%).

The elimination half-life of unchanged carbamazepine in the plasma averages approximately 36 hours following a single oral dose, whereas after repeated administration, which leads to autoinduction of hepatic enzymes, it averages only 16-24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing anti-epileptic agents, half-life values averaging 9-10 hours have been found.

Only 2-3% of the dose, whether given singly or repeatedly, is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active 10, 11-epoxide.

In man, the main urinary metabolite of carbamazepine is the trans-diol derivative originating from the 10, 11-epoxide; a small portion of the epoxide is converted into 9-hydroxymethyl-10-carbamoyl-acridan. Other important biotransformation products are various monohydroxylated compounds, as well as the N-glucuronide of carbamazepine.

The therapeutic range for the steady-state plasma concentration of carbamazepine generally lies between 4-10 mcg/ml.

Indications and Clinical Use

A. Trigeminal Neuralgia:

TEGRETOL (carbamazepine) is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, TEGRETOL has relieved glossopharyngeal neuralgia. For patients who fail to respond to TEGRETOL, or who are sensitive to the drug, recourse to other accepted measures must be considered.

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

B. TEGRETOL has been found useful in:

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

TEGRETOL is not effective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge. Moreover, recent information suggests that exacerbation of seizures may occasionally occur in patients with atypical absences.

Contraindications

TEGRETOL (carbamazepine) should not be administered to patients with a history of hepatic disease or serious blood disorder.

TEGRETOL should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer TEGRETOL to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of TEGRETOL should be low initially, and increased very gradually.

TEGRETOL should not be administered to patients presenting atrioventricular heart block. *(See Sections on Action and Precautions).*

Safe use in pregnancy has not been established. Therefore, TEGRETOL should not be administered during the first 3 months of pregnancy. TEGRETOL should not be given to women of child-bearing potential unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the fetus *(See Reproductive Studies)*. Because of demonstrated toxicity in nursing animals TEGRETOL should not be administered to nursing mothers.

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

Warnings

Although reported infrequently, serious adverse effects have been observed during the use of TEGRETOL (carbamazepine). Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, *thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis* have also been reported. It is, therefore, important that TEGRETOL should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia.

Long-term toxicity studies in rats indicated a potential carcinogenic risk (See Section on "Toxicology"). Therefore, the possible risk of drug use must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

Precautions

Monitoring of Hematological 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. Careful clinical and laboratory supervision should be maintained throughout treatment, including frequent performance of complete blood counts, in order to detect any early signs or symptoms of blood dyscrasia. Should any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, TEGRETOL (carbamazepine) *should be immediately discontinued until the case is carefully reassessed.*

Non-progressive or 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.

Urinary Retention and Increased Intraocular Pressure:

Because of its anticholinergic action, TEGRETOL should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.

Occurrence of Behavioural Disorders:

Because it is closely related to the other tricyclic drugs, there is some possibility that TEGRETOL might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in alcoholics.

Use in Patients with Cardiovascular Disorders:

TEGRETOL should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, an ECG should be performed before administering TEGRETOL, in order to exclude patients with atrioventricular block.

Driving and Operating Hazardous Machinery:

Because dizziness and drowsiness are possible side effects of TEGRETOL, patients should be warned about the possible hazards of operating machinery or driving automobiles.

Drug Interactions:

Induction of hepatic enzymes in response to TEGRETOL may have the effect of diminishing the activity of certain drugs that are metabolized in the liver. This should be considered when administering TEGRETOL concomitantly with other anti-epileptic agents and drugs such as theophylline.

Concomitant administration of TEGRETOL with verapamil, diltiazem, erythromycin, troleandomycin, cimetidine, propoxyphene or isoniazid, has been reported to result in elevated plasma levels of carbamazepine. Since an increase in the blood levels of carbamazepine may result in unwanted effects (e.g. dizziness, headache, ataxia, diplopia and nystagmus may occur), the dosage of carbamazepine should be adapted accordingly and blood levels monitored.

The concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

In patients receiving oral anticoagulant medication, the dosage of the anticoagulant should be readapted to clinical requirements whenever treatment with TEGRETOL is initiated or withdrawn.

TEGRETOL, like other anticonvulsants, may adversely affect the reliability of oral contraceptives. Patients should accordingly be advised to use some alternative, non-hormonal method of contraception.

TEGRETOL, like other psycho-active drugs, may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol consumption during treatment.

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

Adverse Reactions

The reactions which have been most frequently reported with TEGRETOL (carbamazepine) are drowsiness, unsteadiness on the feet, vertigo, dizziness, gastrointestinal disturbances, and nausea. These reactions usually *occur only during the initial phase of therapy. They have rarely necessitated* discontinuing TEGRETOL therapy, and can be minimized by initiating treatment at a low dosage.

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 anti-epileptic drug should be effected under cover of diazepam.

The following adverse reactions have been reported:

Hematologic - Transitory leucopenia, eosinophilia, hyponatremia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.

Hepatic - During the long-term administration of TEGRETOL, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, and hepatitis *have been reported.*

Dermatologic - The following reactions occurred during treatment with TEGRETOL: skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus *erythematosus.*

Neurologic - The reactions reported as occurring during treatment with TEGRETOL include vertigo, somnolence, ataxia, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements and increase in motor seizures. In addition, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, hyperacusis, *and tinnitus have been reported but only very rarely. 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 - Thromboembolism, recurrence of thrombophlebitis in patients with a prior history of thrombophlebitis, primary 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 - Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Elevation of BUN, albuminuria and glycosuria also have been observed.

Respiratory - *Pulmonary hypersensitivity characterized by fever, dyspnea,* pneumonitis or pneumonia.

Gastrointestinal - Disturbances associated with TEGRETOL therapy have included nausea, vomiting, gastric or abdominal discomfort, diarrhea or constipation, anorexia and dryness of the mouth and throat, glossitis and stomatitis.

Ophthalmic - 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 analogy, periodic eye examinations, including slit-lamp fundoscopy and tonometry, are recommended.

Other reactions reported during treatment with TEGRETOL include fever *and chills, aching joints and muscles, leg cramps, conjunctivitis, and* adenopathy or lymphadenopathy.

Symptoms and Treatment of Overdosage

Symptoms of Overdosage:

The symptoms of overdosage include dizziness, ataxia, drowsiness, stupor, nausea, vomiting, restlessness, agitation, disorientation; tremor, involuntary movements, opisthotonos, abnormal reflexes (slowed or hyperactive); mydriasis, nystagmus; flushing, cyanosis, and urinary retention. Hypotension or hypertension may develop. Coma may ensue. EEG and ECG changes may occur. The laboratory findings in isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria.

Treatment of Overdosage:

There is no known specific antidote to TEGRETOL (carbamazepine). Experience with accidental TEGRETOL overdosage is limited. Since TEGRETOL is chemically related to the tricyclic antidepressants, reference to treatment of TOFRANIL (imipramine) overdosage is relevant.

It is recommended that emesis be induced, and that gastric lavage be performed. Vital signs should be watched and symptomatic treatment should be administered as required. Hyperirritability may be controlled by the administration of parenteral diazepam or barbiturates. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient, either in overdosage or in recent therapy (within two weeks).

Barbiturates may also induce respiratory depression, particularly in children. It is therefore advisable to have equipment available for artificial ventilation and resuscitation when barbiturates are employed. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory uepression.

Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids.

It is recommended that the electrocardiogram 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 of TEGRETOL (carbamazepine) with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals whenever possible.

The controlled release characteristics of TEGRETOL CR reduce the daily *fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole* or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid during or after a meal. These controlled release tablets should be prescribed as a twice-daily dosage. If necessary, three divided doses may be prescribed.

Adults and Children Over 12 Years of Age:

Initially, 100 to 200 mg once or twice a day depending on the severity of the *case and previous therapeutic history. The initial dosage is progressively* increased, in divided doses, until the best response is obtained. The usual optimal dosage is 800 to 1200 mg daily. In rare instances some adult patients have received 1600 mg. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Children 6-12 Years of Age:

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

Use in Trigeminal Neuralgia:

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

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

Availability

TEGRETOL Tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Available in bottles of 100 and 500 tablets.

TEGRETOL CHEWTABS 100 mg: Pale pink, round, flat, bevelled-edge tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each chewable tablet contains 100 mg carbamazepine. Available in bottles of 100 CHEWTABS.

TEGRETOL CHEWTABS 200 mg: Pale pink, oval biconvex tablets with distinct red spots. GEIGY engraved on one side and PU engraved on the *other. Fully bisected between the P and U. Each chewable tablet contains* 200 mg carbamazepine. Available in bottles of 100 CHEWTABS.

TEGRETOL CR 200 mg: Beige-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and HC/HC on the other. Fully bisected on both sides. Each controlled release tablet contains 200 mg carbamazepine. Available in bottles of 100 tablets.

TEGRETOL CR 400 mg: Brownish-orange, capsule-shaped, slightly bi*convex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully* bisected on both sides. Each controlled release tablet contains 400 mg carbamazepine. Available in bottles of 100 tablets.

Protect from heat and humidity.

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Geigy
Mississauga, Ontario
L5N 2W5

PAAB CCPP
G88010

Brief Prescribing Information

ANALGESIC
Mersyndol®
WITH CODEINE TABLETS

Indications: For relief of headaches, muscular aches and pains, and neuralgia. Also indicated for relief of cold symptoms.

Contraindications: Hypersensitivity to acetaminophen, codeine, or doxylamine. Pre-existing respiratory depression or embarrassment.

Precautions: Patients should be cautioned not to operate vehicles or hazardous machinery until their response to the drug has been determined. Since the depressant effects of antihistamines are additive to those of other drugs affecting the CNS, patients should be cautioned against drinking alcoholic beverages or taking hypnotics, sedatives, psychotherapeutic agents or other drugs with CNS depressant effects during antihistaminic therapy.

Use with caution in patients with asthma or pulmonary emphysema, in sedated or debilitated patients and those who have undergone thoracotomies or laparotomies. Use in pregnancy is not recommended since codeine phosphate crosses the placental barrier. Prolonged use may have a constipating effect.

Adverse Reactions:

Acetaminophen: The incidence of gastrointestinal upset is less than after salicylate administration. Abnormal liver function has been associated with therapeutic doses ranging from 3 to 8 g per day. In patients with compromised liver function, acetaminophen could exacerbate liver insufficiency. Renal papillary necrosis has been reported following prolonged acetaminophen administration of up to 19 g per day. Rarely, asthmatic attacks have been precipitated. Skin rashes and fixed dermatitis with pruritus have been rarely reported.

Codeine phosphate: Drowsiness, nausea, vomiting and constipation may occur. Infrequent reports of palpitation, pruritus and, rarely, hyperhidrosis and agitation have occurred. Respiratory depression is seen in the higher dosage and habituation or true addiction should be guarded against.

Doxylamine succinate: Drowsiness, vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, irritability, convulsions, urinary retention, or insomnia have been reported.

Dosage: Adults and children over 12 years: 1 to 2 tablets every 4 hours as required. Do not exceed 12 tablets in a 24-hour period.

Availability: Each round, flat, white tablet carries a stylized S and contains: 325 mg acetaminophen; 8 mg codeine phosphate; 5 mg doxylamine succinate. Available in amber glass bottles of 30 and 100 tablets.

Prescribing information available on request.

1. Data on File.
2. Data on File.

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Merrell Dow Pharmaceuticals (Canada) Inc.
380 Elgin Mills Road, East,
Richmond Hill, Ontario. L4C 5H2

PrLIORESAL®

(baclofen)
Muscle relaxant
Antispastic agent

INDICATIONS AND CLINICAL USES

Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Spina 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, 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 lavage). In the obtunded patient, secure the airway with 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
10 mg t.i.d. for 3 days
15 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.

LIORESAL D.S. 20 mg tablet: White to off-white capsule-shaped, biconvex tablets. Engraved GEIGY on one side and GW with bisect on the other.

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

References:
1. Cartlidge, N.E.F., Hudgson, P., Weightman, D.: A comparison of baclofen and diazepam in the treatment of spasticity. J Neurol. Sci. 23: 17-24 (1974).
2. Young, R., Delwaide, P.: Spasticity. New England Journal of Medicine 304: 28-33 & 96-99 (1981).
3. From, A., Heltberg, A.: A double blind trial with baclofen and diazepam in spasticity due to multiple sclerosis. Acta Neurol. Scandinav. 51: 158-166, (1975).

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Geigy
Mississauga, Ontario
L5N 2W5

Cylert*

PEMOLINE

Central Nervous System Stimulant

ACTION: CYLERT (pemoline) is a central nervous system stimulant, which, although structurally different from the amphetamines and methylphenidate, possesses pharmacological activity similar to that of other known stimulants.

Peak serum levels after single doses are reached within 2 to 4 hours and the serum half-life is approximately 12 hours. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days.

INDICATIONS AND CLINICAL USES: CYLERT (pemoline) is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Attention Deficit Disorder and Hyperkinetic Syndrome are among the terms being used to describe the above signs and symptoms. In the past, a variety of terms has been associated with these signs and symptoms including: Minimal Brain Dysfunction, Hyperkinetic Reaction of Childhood, Hyperkinetic Syndrome, Hyperactive Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction.

CONTRAINDICATIONS: CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. (See ADVERSE REACTIONS).

WARNINGS: CYLERT (pemoline) is not recommended for children less than 6 years of age since its safety and efficacy in this age group have not been established.

Clinical experience suggests that in psychotic children, administration of pemoline may exacerbate symptoms of behavior disturbance and thought disorder.

Data are inadequate to determine whether chronic administration of pemoline may be associated with growth inhibition; therefore, growth should be monitored during treatment.

PRECAUTIONS: Drug treatment is not indicated in all cases of the behavioral syndrome characterized by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. It should be considered only in light of the complete history and evaluation of the child. The decision to prescribe CYLERT (pemoline) should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with pemoline is usually not indicated.

Long-term effects of pemoline in children have not been well established.

Liver function tests should be performed prior to and periodically during therapy with pemoline. The drug should be discontinued if abnormalities are revealed and confirmed by follow-up tests. (See ADVERSE REACTIONS regarding reports of abnormal liver function tests and jaundice).

Pemoline should be administered with caution to patients with significantly impaired hepatic or renal function.

The interaction of pemoline with other drugs has not been studied in humans. Patients who are receiving pemoline concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

Pemoline failed to demonstrate a potential for self-administration in primates. However, the pharmacologic similarity of pemoline to other psychostimulants with known dependence liability suggests that psychological and/or physical dependence might also occur with pemoline. There have been isolated reports of transient psychotic symptoms occurring in adults following the long-term misuse of excessive oral doses of pemoline. Pemoline should be given with caution to emotionally unstable patients who may increase the dosage on their own initiative.

Usage during Pregnancy and Lactation: The safety of pemoline for use during pregnancy and lactation has not been established. (See REPRODUCTION AND TERATOLOGY). Although central nervous system stimulants are seldom indicated after puberty, it should be borne in mind that pemoline should not be used during pregnancy or in women who may become pregnant.

ADVERSE REACTIONS: Insomnia is the most frequently reported side effect of CYLERT (pemoline); it usually occurs early in therapy, prior to an optimum therapeutic response. In the majority of cases it is transient in nature or responds to a reduction in dosage.

Anorexia with weight loss may occur during the first weeks of therapy. In the majority of cases it is transient in nature; weight gain usually resumes within three to six months.

Stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations have been reported.

Elevations of SGOT, SGPT, and serum LDH have occurred in patients taking pemoline, usually after several months of therapy. These effects appear to be reversible upon withdrawal of the drug, and are thought to be manifestations of a delayed hypersensitivity reaction. There have also been a few reports of jaundice occurring in patients taking pemoline; a causal relationship between the drug and this clinical finding has not been established.

The following CNS effects have been reported with the use of pemoline: dyskinetic movements of the tongue, lips, face and extremities, nystagmus and nystagmoid eye movements, and convulsive seizures. Central nervous system stimulants have been reported to precipitate attacks of Gilles de la Tourette syndrome.

Mild adverse reactions appearing early during the course of treatment with pemoline often remit with continuing therapy. If adverse reactions are of a significant or protracted nature, dosage should be reduced or the drug discontinued.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Signs and symptoms of acute CYLERT (pemoline) overdosage may include agitation, restlessness, hallucinations, dyskinetic movements and tachycardia. The treatment for an acute overdosage of pemoline is essentially the same as that for an overdosage of any CNS stimulant. Management is primarily symptomatic and may include induction of emesis or gastric lavage, sedation, and other appropriate supportive measures.

Results of studies in dogs indicate that extracorporeal hemodialysis may be useful in the management of pemoline overdosage; forced diuresis and peritoneal dialysis appear to be of little value.

DOSAGE AND ADMINISTRATION: CYLERT (pemoline) is administered as a single oral dose each morning. The recommended starting dose is 37.5 mg/day. This daily dose should be gradually increased by 18.75 mg at one week intervals until the desired clinical response is obtained. The effective daily dose for most patients will range from 56.25 to 75 mg. The maximum recommended daily dose of pemoline is 112.5 mg.

Clinical improvement with pemoline is gradual. Using the recommended schedule of dosage titration, significant benefit may not be evident until the third or fourth week of drug administration.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Hyperactivity diminishes with age to the point where it remains a serious problem in only a minority, although other major handicaps may be present. Usually, by puberty the need for medication has diminished or is no longer required.

AVAILABILITY: CYLERT (pemoline) is supplied as monogrammed, grooved tablets in two dosage strengths:
37.5 mg tablets (orange-colored)
in bottles of 100 (List 6057); and
75 mg tablets (tan-colored) in bottles of 100 (List 6073).

CHEMISTRY AND PHARMACOLOGY: CYLERT (pemoline) is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one.

Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg/mL) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg/mL.

Pemoline has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby pemoline produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. Pemoline is excreted primarily by the kidneys; approximately 75% of an oral dose is recovered in the urine within 24 hours. Approximately 43% of pemoline is excreted unchanged.

TOXICOLOGY

Acute Toxicity:
The LD_{50} of magnesium pemoline in mice was 500 mg/kg (= 375 mg/kg pemoline) orally and 487 mg/kg (= 365 mg/kg pemoline) intraperitoneally. In rats, the oral LD_{50} was 581 mg/kg (= 436 mg/kg pemoline) and the intraperitoneal LD_{50} was 497 mg/kg (= 373 mg/kg pemoline). The oral LD_{50} in monkeys was 450 mg/kg (= 338 mg/kg pemoline). Principal signs observed were hyperactivity, increased muscle tone, biting, gnawing, squealing, mydriasis and piloerection. Death was often preceded by ataxia, labored breathing and respiratory paralysis.

Long-Term Toxicity:
A six-month oral toxicity study was conducted in 16 dogs at doses of 0, 2, 5 and 10 mg/kg/day of magnesium pemoline (0, 1.5, 3.8, and 7.5 mg/kg/day of pemoline). Signs observed were those of central nervous system stimulation, characterized by moderate hyperactivity, hyperirritability and increased sensitivity to normal background noises or distractions. The severity of these signs was dose-related and diminished or disappeared with the passage of time, indicating the development of tolerance to the stimulant effects.

A 46-week oral toxicity study was conducted in rats at doses of 0, 2.5, 35 and 100 mg/kg/day of magnesium pemoline (0, 1.9, 26.3 and 75 mg/kg/day of pemoline). Early in the test, the animals in all drug groups displayed dose-related hyperactivity and increased sensitivity to external stimuli. These effects gradually subsided and disappeared after 2 to 3 weeks, indicating development of tolerance. At 6 and 9 months, a significant increase was observed in the incidence of mortality in the high-dose group compared to the control group. Similar but less marked trends were found in the middle-dose group at these time intervals. A 66-week study in female rats resulted in a cumulative maximal consumption of 0.3 g and 5.8 g/rat of pemoline after oral doses of 0, 5 and 100 mg/kg/day of magnesium pemoline (0, 3.8 and 75 mg/kg/day of pemoline). The growth rate in the low dosage group approximated that of the controls, while the high dosage group exhibited some retardation of growth during the first 46 weeks, showing average growth during the final 20 weeks of the study, when magnesium pemoline was not present in the diet.

REPRODUCTION AND TERATOLOGY: Standard studies of fertility, teratology and reproduction were conducted in rats and rabbits. Daily oral doses of magnesium pemoline of 25 and 50 mg/kg (18.75 and 37.5 mg/kg of pemoline) beginning at conception produced no abnormalities in the fetuses and did not affect viability at birth, although postnatal survival of pups was impaired. Further studies using similar dose levels with drug administration beginning 14 days before conception demonstrated an increased incidence of stillbirths and cannibalization. A significantly lower postnatal survival of pups occurred at the 50 mg/kg dose level, with similar but less marked effects noted at the 25 mg/kg level. There is some indication that the impaired survival of pups was drug related.

REFERENCES

1. Connors CK, Taylor E. Pemoline, Methylphenidate, and Placebo in Children with Minimal Brain Dysfunction. Arch Gen Psych 1980; 37:922-930.
2. Weinberg F. Symposium on Clinical Applications of Pemoline in Attention Deficit Disorder. February 1987, Toronto.
3. Dulcan MK. Attention Deficit Disorder: Evaluation and Treatment. Pediatric Annals 1985; 14(5):383-400.
4. Langer DH, Sweeney KP, Bartenbach DE, Davis PM, Menander KB. Evidence of Lack of Abuse or Dependance Following Pemoline Treatment: Results of a Retrospective Survey. Drug and Alcohol Dependence 1986;17:213-227.

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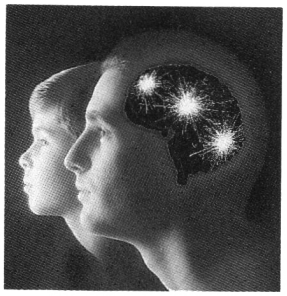

℞Depakene* ℞Epival*

valproic acid — divalproex sodium

ACTION Valproic acid and divalproex sodium are chemically-related anticonvulsants. Although their mechanism of action has not yet been established, it has been suggested that their activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown. Epival (divalproex sodium) 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 ½) 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 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.

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 WARNINGS section regarding statement on fatal hepatic dysfunction.

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

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

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

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

If DEPAKENE* (valproic acid) is to be used in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival or Depakene.

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

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

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

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

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

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

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

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

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

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

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

PRECAUTIONS: Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

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

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

Because Depakene or Epival 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.

Depakene and Epival are partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

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

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

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

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

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

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

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

Caution is recommended when valproic acid or divalproex sodium is administered with drugs affecting coagulation, e.g. 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 (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). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

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

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 Depakene or 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.

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

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

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

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

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

AVAILABILITY Depakene (valproic acid) is available as orange-coloured, soft gelatin capsules of 250 mg in bottles of 100 capsules; pale yellow, oval, soft gelatin enteric-coated capsules of 500 mg in bottles of 100 capsules; and as a red syrup containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL in bottles of 450 mL.

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

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

kg	lb	Total daily dose (mg)	Dosage 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

Product monograph available on request.

1. Henriksen O, Johannessen SI. Clinical and pharmacokinetic observations on sodium valproate – A 5-year follow-up study in 100 children with epilepsy. Acta Neurol Scand 1982;65:504-523.
2. Delgado-Escueta AV et al. The Treatable Epilepsies. New Engl J Med 1983;308(26):1576-1584.
3. Turnbull DM et al. A comparison of phenytoin and valproate in previously untreated adult epileptic patients. J Neuro Neurosurg Psych 1982; 45:55-59.
4. Chadwick DW. Valproate Monotherapy in the Management of Generalized and Partial Seizures. Epilepsia 1987;28(2):S12-S17.
5. Wilder BJ et al. Gastrointestinal tolerance of divalproex sodium. Neurology 1983;33(6):808-811.
6. Loiseau P. Rational Use of Valproate: Indications and Drug Regimen in Epilepsy. Epilepsia 1984;25(1):S65-S72.
7. American Academy of Pediatrics Committee on Drugs. Behavioural and Cognitive Effects of Anticonvulsant Therapy. Pediatrics 1985; 76(4):644-647.
8. Beghi E et al. Adverse Reactions to Antiepileptic Drugs: A Multicenter Survey of Clinical Practice. Epilepsia 1986;27(4):323-330.

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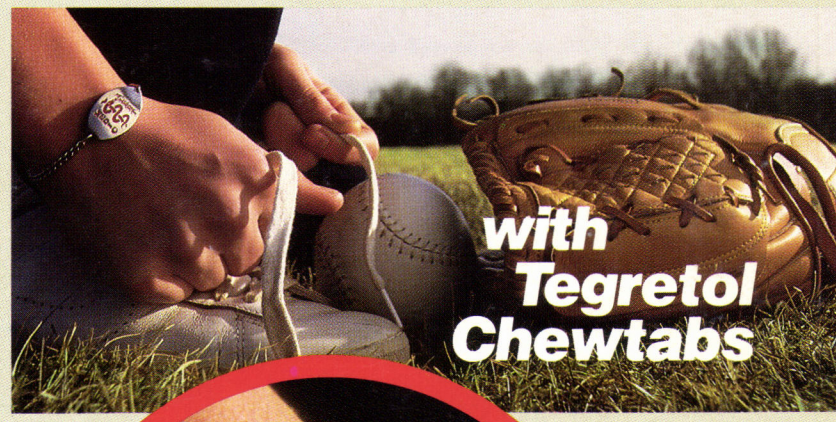

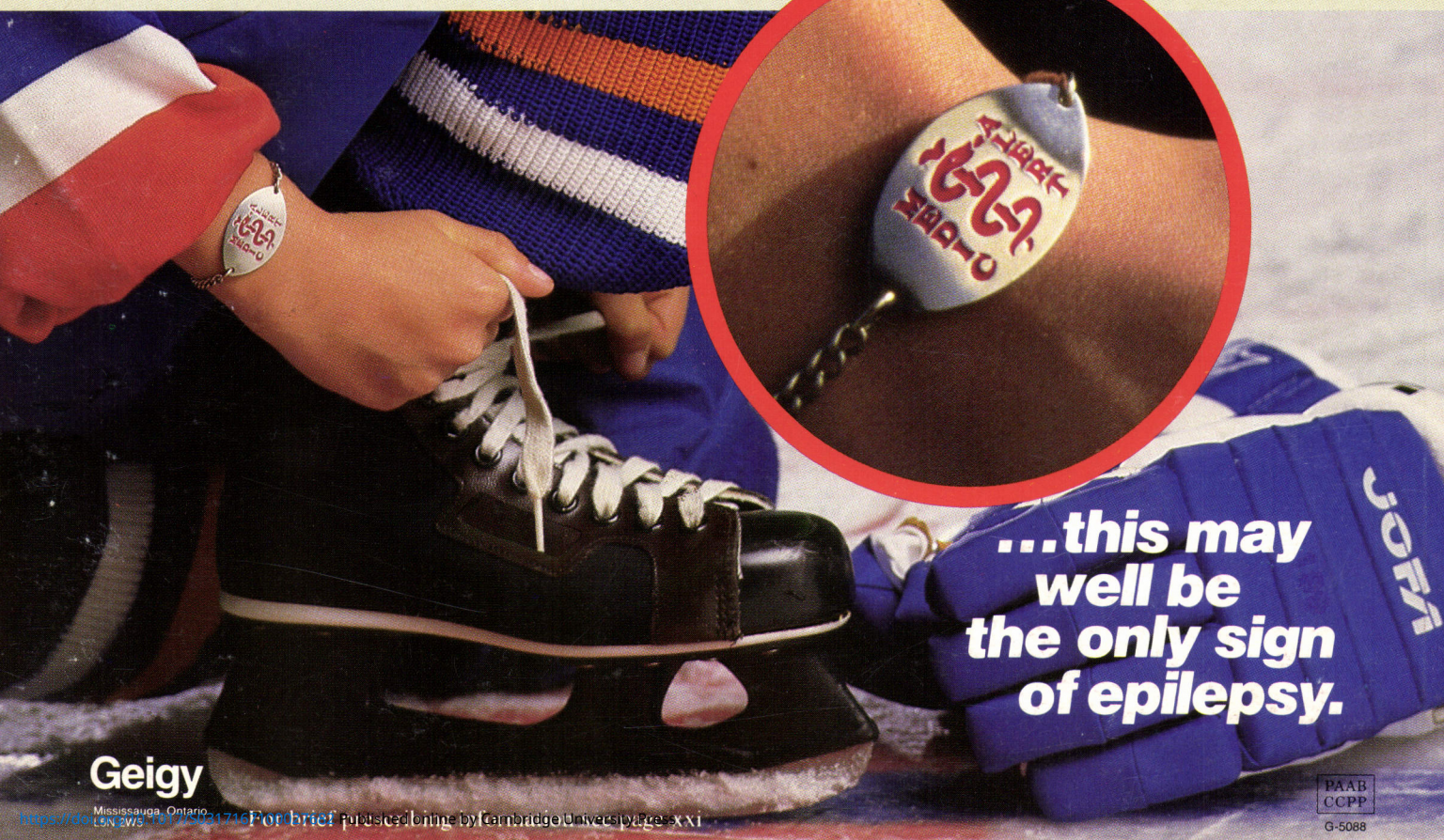

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