BLioresal

(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

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, talerability to the drug.

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 substain 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

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

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

Symptoms and Treatment of Overdosage
Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, 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).

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).

40-but nig 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).

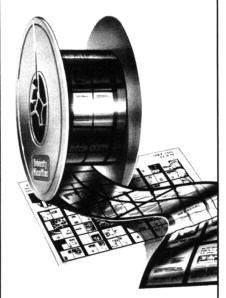
Availability LIORESAL (baclofen) 10 mg tablets

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.

This publication īs available in microform.



University Microfilms International reproduces this publication in microform: microfiche and 16mm or 35mm film. For information about this publication or any of the more than 13,000 titles we offer, complete and mail the coupon to: University Microfilms International, 300 N. Zeeb Road, Ann Arbor, MI 48106. Call us toll-free for an immediate response: 800-521-3044. Or call collect in Michigan, Alaska and Hawaii: 313-761-4700.

☐ Please send information about these titles:				
		_		
Name				
Company/Institution _				
Address				
City				
State	Zip	_		
Phone ()		_		

University Microfilms International

MOVING?

PLEASE NOTIFY US OF YOUR **CHANGE OF ADDRESS IN** ADVANCE.

PASTE OLD ADDRESS LABEL **HERE**

NEV	V A	DD	RE	SS:
-----	-----	----	----	-----

NAME:								
(LAST) (FIRST) (MIDDLE INITIAL)								
STREET ADDRESS:								
CITY:								
PROVINCE/STATE:								
COUNTRY:								
POSTAL/ZIP CODE:								

MAIL TO:

Subscriptions. **CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES Faculty of Medicine University of Calgary** 3330 Hospital Drive N.W. Calgary, Alberta, Canada T2N 4N1

(xv)

G-3017

Evomatic 8000

- completely integrated system for evoked potential testing

- ★ Galvanically isolated patient unit
- ★ One preamplifier for each electrode
- ★ Fully computerized operation
- ★ Powerful signal averaging and data processing
- ★ 60 user-defined programs stored on one disc
- ★ Color display combined with finger-touch opera-

- ★ Multi-functioning stimulators for auditory, visual and somatosensory evoked
- ★ Storage of full patient journal including curves, patient data and text
- ★ Eight color plotter printouts
- ★ Built-in IEEE-488 inter-
- ★ Expandable from 1 to 8 channels



NEUROMUSCULAR FELLOWSHIP

At least 1 year, beginning in July 1986. Comprehensive experience in clinical, electrophysiological, morphological and animal research aspects of neuromuscular disease at University and Victoria Hospitals. Salary through grant support based on research project.

Send Curriculum Vitae and three references to:

Dr. T.E. Feasby,
Department of Clinical Neurological Sciences,
The University of Western Ontario,
University Hospital,
P.O. Box 5339, Stn. A.,
London, Ontario, Canada
N6A 5A5

Behavioural Neurology Fellowship

Available January 1, 1986

One year comprehensive clinical training program in Behavioural Neurology on 20 bed Neurobehavioural Unit at Baycrest Centre For Geriatric Care. Research opportunities available.

Reply with CV to:

Dr. Morris Freedman Mount Sinai Hospital Suite 433 600 University Avenue Toronto, Ontario Canada M5G 1X5

Neuropathologist

A senior faculty position is available in the Department of Pathology (Division of Neuropathology) at the Toronto Western Hospital, a major teaching hospital of the University of Toronto. This is a second Neuropathology position, newly created, to allow development of a strong research program in Neuropathology. A milieu for interactive research is provided by a large group of basic and clinical neuroscientists, now established at the hospital. The position calls for an individual with well-developed leadership skills and a commitment to academic neuropathology.

The level of academic appointment and salary are dependent upon qualification and experience. In accordance with Canadian immigration requirements, preference will be given to Canadian citizens and landed immigrants. Application should include a cirriculum vitae, a summary of research interests, and the names of four references.

They should be submitted to:

Mr. C. Hunt
President
Toronto Western Hospital
399 Bathurst Street
Toronto, Ontario
M5G 2S8

ADVERTISER'S INDEX

Abbot Laboratories (Epival) - xix, xx

Ciba/Geigy

Lioresol — x, xv

Tegretol — obc, ix

Dantec Electronics Ltd.

Evomatic 8000 — xvi

Neuromatic 2000 — viii

Dr. Morris Freedman, M.D. (Classified) — xvii

Nicolet Instrument Canada Inc. - xi

Parke-Davis Canada Inc. (Dilantin) — ibc, xii

Sunnybrook Hospital (Classified) -- xii

Sandoz Canada Inc.

Cafergot - xiv

Fiorinal — vii

Parlodel — ifc, ii, iii, iv

Toronto Western Hospital (Classified) — xvii

University Hospital (Classified) - xvii

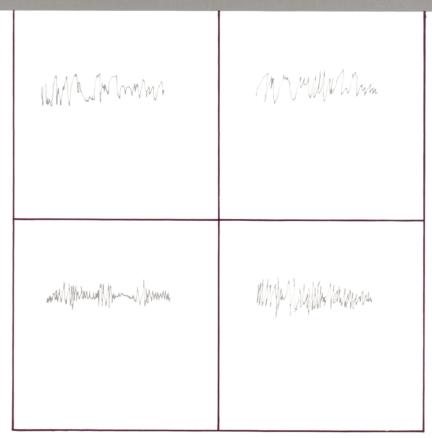
Unimed Pharmaceutical (Serc) - vi

University of Calgary (Classified) - xvi

Wild Lietz (M600) Series — xiii



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. Three strengths are available, including a 125-mg tablet that is small enough for children to swallow easily.

in absence or tonic-clonic seizures



a better life for more epileptic patients

l. Wilder BJ et al. Clin Pharmacol Ther 1983, (34)4:501-504.





ACTION: Epival (divalproex sodium) has anticonvulsant pro perties, 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 dissociales into valproic acid in the gastrointestinal tract. Peak serum levels of valproic acid occur in 3 to 4 hours.

The serum half-life (1,2) of valproic acid is typically in the range of δ to δ 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 $100~\mu g/mL$. 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

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

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 fonic-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 dystunction. It is contraindicated in patients with known sensitivity to the drug.

wARNINGS. Hepatic failure resulting in tatalities 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 lests 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 lests may not be abnormal in all in-stances, 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 dystunction has progressed in spite of discontinuation of drug. The trequency of adverse ef-fects 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 en at higher dosages.

seen at higher dosages. Use in Pregnancy. According to recent reports in the medical literature, valproic acid may produce leratogenicity in the off-spring of human females receiving the drug during pregnancy. The incidence of neural lube defects in the felus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was restingted that the risk of valproic acid expressed upone pay. estimated that the risk of valproic acid exposed women hav-ing children with spina bitida 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 temales 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 told. The increase is largely due to specific detects, eg., congenital malformations of the heart, cleft lip and/or palate, and neural tube detects. 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 fac-tors, 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

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).

Fortility. Chronic loxicily 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 ter-tility 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 develop ment 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

PRECAUTIONS: Hepatic dysfunction: See CONTRAINDICA-TIONS 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. Its is recommended that pa-tients receiving Epival (divalproex sodium) be monitored tor 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 vallaria cold and phenytoin. 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 drug.**

Drug Interactions: Epival (divalproex sodium) may potentiate the drug that the drug that

tiate 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) pheny-toin 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., acetyl-salicylic acid and warfarin (See ADVERSE REACTIONS).

ADVERSE REACTIONS: The most commonly reported adverse

reactions are nausea, vomiling 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. Alaxia, 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 pelechiae have rarely been noted. **Endocrine**: There have been reports of irregular menses and secondary amenorthea in patients receiving valproic

Abnormal thyroid function tests have been reported (See PRECAUTIONS)

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

Musculoskeletal: Weakness has been reported

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggrega-tion (See PRECAUTIONS). This may be reflected in altered bleeding time Bruising, hematoma formation and trank hemorrhage have been reported. Relative lymphocytosis and hypotibrinogenemia 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 trequent 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 tatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occuring 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 par-ticular attention to the prevention of hypovolemia and the

mainlenance of adequate uninary output. **DOSAGE 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)

Weight Total daily		equivalent to valoroic acid			
kg	lb_	dose (mg)	Dose l	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

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. The tablets should

be swallowed without chewing.

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.

ANOTHER UNEVENTFUL DAY.

DILANTIN (phenytoin)

Start with it. Stay with it.

DILANTIN* (phenytoin) is a drug of first choice for controlling generalized tonic clonic seizures.

No other antiepileptic is more widely prescribed.

No other antiepileptic has been the subject of more extensive clinical studies2

And no other antiepileptic boasts a more simplified medication schedule. The slow absorption of Dilantin Capsules allows a single daily dose for maintenance therapy in many adults, once the divided dose of three 100 mg capsules has adequately controlled seizures.

References: 1. CDTI 2. Goodman and Gilman, Sixth Edition.

*Reg. T.M. Parke, Davis & Company, Parke-Davis Canada Inc., auth. user

New Tegretol® Chewtabs (carbamazepine)

100mg and 200mg*

- the only chewable carbamazepine
- easier titration for both children and adults
- increased convenience provided by an easily administered chewable formulation
- improved compliance arising from a pleasant tasting cherry-mint flavour

Now indicated in children aged 6 years and over

Geigy

