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# THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES

# LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES



Index to Volume 6

Official Journal of the Canadian Neurological Society, the Canadian Neurosurgical Society and the Canadian Society of Electroencephalographers, Electromyographers and Clinical Neurophysiologists.

VOLUME 6 NO. 4 — INDEX NOVEMBER 1979

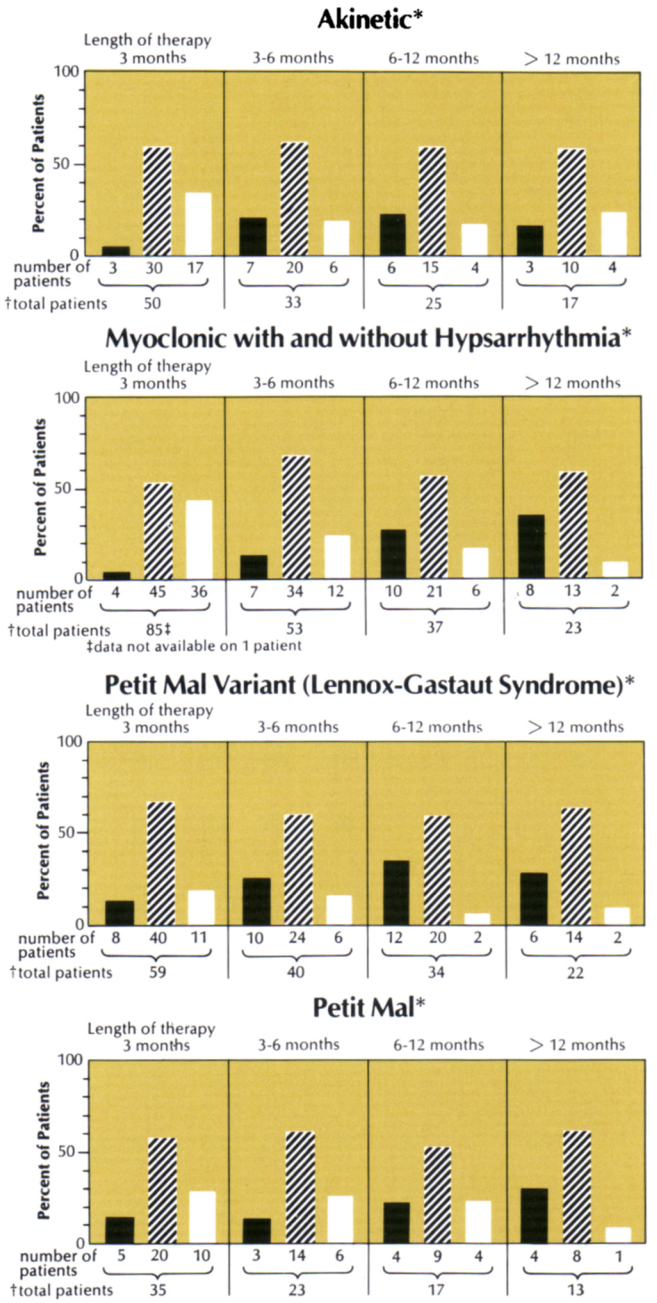
# Rivotril®

# Oral anticonvulsant therapy from 'Roche' research

RIVOTRIL, with specific and potent anticonvulsant properties, is a new benzodiazepine in the same family as Librium®, Valium® and Dalmane® Roche®. It is therefore characterized by the same high degree of safety and efficacy.

- used alone or as an adjunct, RIVOTRIL can reduce the frequency and/or severity of akinetic, myoclonic and petit mal variant (Lennox-Gastaut syndrome) seizures.
- it may be of value as principal medication in petit mal where succinimide therapy has failed.
- the most frequently noted side effects, drowsiness and ataxia, generally are dose related and can often be controlled by dosage adjustments.

## Effect of RIVOTRIL on seizure frequency




■ Seizures 100% controlled
▨ Seizures better than 50% reduced in frequency
□ Seizures uncontrolled

*Data on file, Hoffmann-La Roche Limited

†Patients dropped from the study for a variety of reasons as well as those treated for less than 12 months account for the decrease in total patient population.

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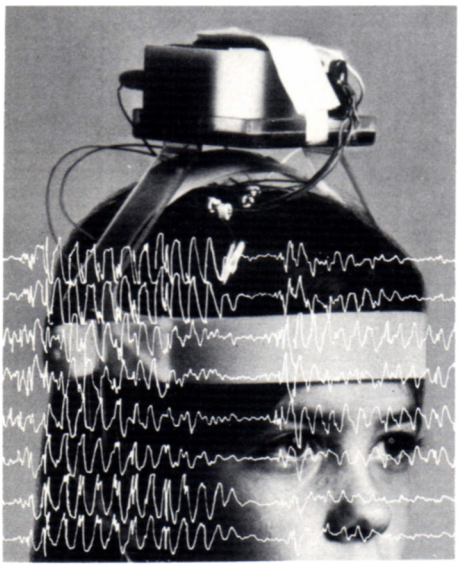
# An important aid in the management of minor seizures



Noninvasive EEG telemetry device used to monitor patients in studies evaluating RIVOTRIL.

## Rivotril® (clonazepam)

### Brief Prescribing Information

**Action**

RIVOTRIL is a benzodiazepine and has sedative, hypnotic, and anticonvulsant properties characteristic of this class of drugs. As an anticonvulsant, it decreases the frequency, amplitude, duration, and spread of discharges in minor motor seizures and suppresses the spike-and-wave discharge in absence seizures.

The maximum blood level of clonazepam after a single oral dose is reached within 1 to 2 hours. The half-life of clonazepam is approximately 18 to 50 hours, and the main route of excretion is in the urine.

**Indications**

RIVOTRIL has been found useful when used alone or as an adjunct in the management of myoclonic and akinetic seizures and petit mal variant (Lennox-Gastaut syndrome).

RIVOTRIL may also be of value in patients with petit mal (absence spells) who have failed to respond satisfactorily to succinimides.

If a loss of anticonvulsant effect occurs, dosage adjustment may re-establish efficacy in some cases.

**Contraindications**

In patients with:

- known hypersensitivity to benzodiazepines
- significant liver disease
- narrow-angle glaucoma

**Warnings**

RIVOTRIL should be used by women of child-bearing potential only when the expected benefits to the patient warrant the possible risks to the fetus. Women who become pregnant should consult their physician promptly with regard to continuing antiepileptic medication.

Mothers receiving RIVOTRIL should not breast feed their infants.

Because adverse effects may possibly become apparent only after years of administration, a risk/benefit consideration of long-term use of RIVOTRIL is important in pediatric patients.

**Precautions**

The use of multiple anticonvulsants may increase CNS-depressant effects and the dosage of each drug may need adjustment to obtain the optimum effect.

To avoid precipitation of status epilepticus, abrupt withdrawal of RIVOTRIL must be avoided. Substitution of another anticonvulsant may be indicated during RIVOTRIL withdrawal.

In a very few patients, RIVOTRIL may cause a paradoxical increase in seizure activity or new types of seizures. RIVOTRIL may precipitate the onset of grand mal or increase its incidence. The addition of appropriate anticonvulsants or an increase in their dosage may be necessary.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and should also be warned against the concomitant use of alcohol or other CNS-depressant drugs.

Patients who may be prone to increase drug dosage on their own should be monitored carefully when receiving RIVOTRIL, as benzodiazepines have produced habituation, dependence, and withdrawal symptoms.

RIVOTRIL should be administered with caution to patients with impaired renal function.

Periodic liver function tests and blood counts are recommended during long-term therapy with RIVOTRIL.

Treatment with RIVOTRIL should be instituted with caution in patients with chronic respiratory disease, because of the possibility of hypersecretion in the upper respiratory passages.

**Adverse reactions**

Drowsiness has occurred in 50% and ataxia in 30% of the patients treated with RIVOTRIL. In some cases these effects have diminished with time. Behaviour problems have been noted in approximately 25% and increased salivation in 7% of the patients.

Please see product monograph for a complete list of other possible adverse reactions.

**Dosage and administration**

Dosage of RIVOTRIL must be determined for each patient according to clinical response and tolerance. Dosage depends, above all, on the age of the patient.

The daily requirement should be given in 2 or 3 divided doses. If the doses are not equal, the larger dose should be given before retiring.

*Children up to 10 years or 30 kg:* In order to minimize drowsiness, the initial dosage should usually be between 0.01 and 0.03 mg/kg/day and must not exceed 0.05 mg/kg/day.

The dosage should be increased by 0.25 to 0.5 mg/day every third day, unless seizures are controlled or side effects intervene, until a maintenance dosage of 0.1 to 0.2 mg/kg/day has been reached.

*Adults:* The initial dosage should not exceed 1.5 mg/day.

The dosage should be increased by 0.5 to 1 mg every third day, until seizures are controlled or side effects intervene. The recommended maintenance dosage for adults is 8 to 10 mg/day in 3 divided doses. Dosages in excess of 20 mg/day should be administered with caution.

Whenever RIVOTRIL is added to an anticonvulsant regimen, it should be borne in mind that the use of multiple anticonvulsants may result in increased depressant adverse effects.

**Supply**

Scored tablets, 0.5 and 2 mg. Bottles of 100.

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Full prescribing information on request.

ROCHE

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Vaudreuil, Quebec



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THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES
LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES



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Papers will be accepted in French or English. All papers should be accompanied by a short résumé in both languages. The résumé translation will be done by the editorial board if requested.

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REFERENCES to authors outside the context of the sentence should read (Name, Year). *i.e. "However, a recent study (Bird and Iverson, 1975) showed a decreased, etc."* Authors mentioned within the context of the sentence should read Name (Year). *"i.e. ... twenty years since Ecker and Reimenshender (1951) demonstrated, etc."* References should be typed in alphabetical order on a separate sheet and include author's name, initials, year, title, publication, volume, first and last page, i.e. Isacson, P. (1967). Myx-oviruses and autoimmunity. Progress in Allergy, 10, 256-292. Abbreviations should be the same as those used in Cumulated Index Medicus.

Textbook references should include name of text, author's name, page number, publisher and city.

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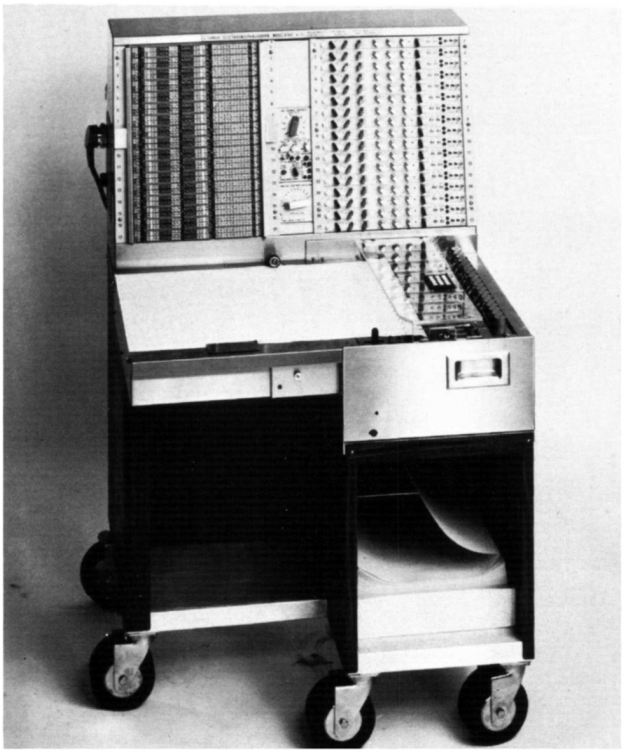

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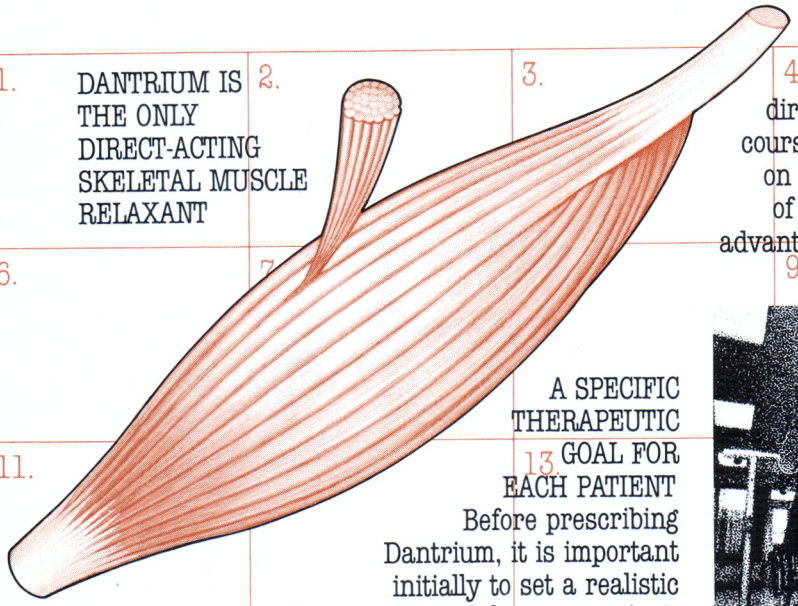
# THE DANTRIUM® CONCEPT

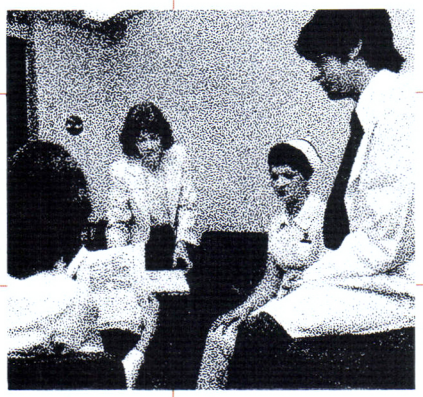
DANTRIUM IS THE ONLY DIRECT-ACTING SKELETAL MUSCLE RELAXANT



For chronic spasticity, direct action is often the best course.[1] Dantrium acts directly on the contractile mechanism of skeletal muscle. Its unique advantages can bring substantial relief to many patients.[2]

## A SPECIFIC THERAPEUTIC GOAL FOR EACH PATIENT

Before prescribing Dantrium, it is important initially to set a realistic therapeutic goal for your patient. As progress is gradual, continual assessment is vital.



| Response | | Adults | Children |
|---|---|---|---|
| Initial, transient side effects often encountered | 1st week | 25 mg once daily | 1.0 mg/kg once daily |
| | 2nd week | 25 mg BID | 1.0 mg/kg BID |
| Response range for most patients | 3rd week | 25 mg QID | 1.0 mg/kg QID |
| | 4th week | 50 mg QID | 2.0 mg/kg QID |
| | 5th week | 75 mg QID | 3.0 mg/kg QID |
| | 6th week | 100 mg QID | |

The titration chart shows the flexibility of Dantrium. Dosage is initiated at a low level and titrated according to individual response. If benefits are not evident in 45 days, therapy should be discontinued.

Dantrium avoids persistent sedation, the major limitation of centrally acting muscle relaxants.[4,5] With Dantrium, drowsiness "...usually disappears within a few days, and it can often be avoided by starting treatment with small dosages to be increased at weekly intervals."[4] However, it can be used concomitantly with a reduced dosage of a CNS agent to achieve maximum results. It is a major breakthrough in the treatment of chronic spasticity.[6]

## TEAMWORK MAKES THE DIFFERENCE

Every member of the health care team should be aware of the patient's therapeutic goal. The attending specialist, physio/occupational therapists and nursing staff can then work together in a constant feedback situation, all helping with each physical and psychological step forward. Teamwork makes The Dantrium Concept the most viable answer to many forms of chronic spasticity.[3]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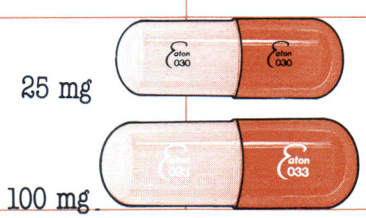
3. Chyatte SB, Birdsong JH, Roberson DL: Dantrolene sodium in athetoid cerebral palsy. Arch Phys Med Rehabil 54:365-368, 1973.
4. Mayer N, Mecomber SA, Herman R: Treatment of spasticity with dantrolene sodium. Am J Phys Med 52:18-29, 1973.
5. Steinberg FU, Ferguson KL: J Am Geriatr Soc 23:70-73, 1975.
6. Keenan RE, Kolb ME, Horne ML: Collaborative comparison of dantrolene sodium and diazepam. Clinical Therapeutics 1:48-55, 1977.



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Pr

# Dantrium®

(dantrolene sodium capsules)

## ACTIONS

Recordings of muscle tensions and electrical activity in both animal and man suggest that Dantrium has a direct inhibitory effect on the development of contractile tension. Spastic patients receiving Dantrium have shown a 40-70% reduction in the skeletal muscle tension induced by direct electrical stimulation of the motor nerve with no alteration of the EMG. This decrease in contractile tension can be attributed to an effect of Dantrium beyond the myoneural junction. Total paralysis does not occur since the Dantrium-induced change in the contractile state of skeletal muscle is limited in magnitude. The reduction in contractile activity accounts for the ability of Dantrium to diminish spasticity resulting from pathological states associated with a hyperactive stretch reflex.

Dantrium also produces central nervous system effects resulting in such manifestations as drowsiness, dizziness and generalized weakness.

Absorption of Dantrium is slow, dose-related blood levels are obtained which peak in 4 to 6 hours after a single oral dose. The peak pharmacologic effect generally occurs in 1½ to 3 hours at concentrations of 50 to 75 percent of the peak plasma level. Dantrium is highly bound to plasma protein and, to a lesser extent, red blood cells. Metabolism is rapid via hepatic microsomal enzymes. The major metabolites in humans are a 5-hydroxy analog and an acetamino analog. Urinary excretion of Dantrium and metabolites occurs in an initially rapid phase (t-½, 2.5 to 3 hours) followed by a slower phase over a 24 hour period. Dantrium is also removed by biliary excretion.

## INDICATIONS

Dantrium is useful in controlling the manifestations of chronic spasticity of skeletal muscle resulting from such conditions as spinal cord injury, cerebral palsy, multiple sclerosis, and stroke, whenever such spasticity results in a decrease in functional use of residual motor activity. Dantrium is not indicated in the relief of skeletal muscle spasms due to rheumatic disorders.

## CLINICAL USES

Dantrium has been studied in the treatment of selected patients with moderate to severe skeletal muscle spasticity resulting from stroke, spinal cord injury, cerebral palsy, multiple sclerosis, and other neuropathies. It seems to act directly on the skeletal muscle and has been found useful whenever manifestations of spasticity such as increased muscular resistance to stretch, clonus, and exaggerated reflex posturing interfere with therapeutic exercise programs, utilization of braces, transfer manoeuvres, posture equilibrium, ambulation, and activities of daily living.

Marked reduction or even cessation of spontaneous involuntary movements was observed in many patients receiving Dantrium. The extent to which Dantrium may contribute toward improvement in spasticity and activities in daily living can be tested by withdrawing the drug for 2 to 4 days and observing whether an exacerbation of the patient's condition occurs.

## CONTRAINDICATIONS

Skeletal muscle spasticity without suitable volitional activity (residual motor activity) may be of value in a rehabilitation program aimed toward sustaining upright posture and balance, and may assist a patient's locomotor pattern. Relief of such spasticity would reduce rather than increase function. Therefore, in cases where spasticity is utilized to obtain or maintain increased function, Dantrium is contraindicated.

Dantrium is contraindicated in patients with compromised pulmonary function, particularly those with obstructive pulmonary disease.

## WARNINGS

DANTRIUM (DANTROLENE SODIUM) HAS THE POTENTIAL TO PRODUCE HEPATOTOXICITY AND SHOULD NOT BE USED IN CONDITIONS OTHER THAN THOSE RECOMMENDED. CASES OF FATAL HEPATITIS HAVE BEEN REPORTED IN PATIENTS WHO HAD RECEIVED DANTRIUM FOR SIXTY DAYS OR LONGER. SYMPTOMATIC HEPATITIS AND LABORATORY EVIDENCE OF LIVER DYSFUNCTION HAVE ALSO BEEN REPORTED IN A NUMBER OF PATIENTS RECEIVING DANTRIUM. SOME CASES OF HEPATITIS WERE CONSIDERED TO BE DIRECTLY RELATED TO DANTRIUM ADMINISTRATION, WHEREAS OTHERS MAY HAVE BEEN DUE TO OTHER CAUSES. DANTRIUM-INDUCED HEPATOTOXICITY APPEARS TO OCCUR IN APPROXIMATELY ONE PERCENT OF THE PATIENTS RECEIVING THE DRUG. DANTRIUM MAY EXACERBATE PRE-EXISTING LIVER DYSFUNCTIONS. NO SERIOUS HEPATIC INJURY HAS YET BEEN REPORTED IN PATIENTS RECEIVING THE DRUG FOR LESS THAN 60 DAYS. ALTHOUGH LIVER ENZYME ELEVATIONS HAVE OCCURRED, RISK OF HEPATIC INJURY APPEARS TO BE GREATER IN FEMALES AND IN PATIENTS OVER 35 YEARS OF AGE. THEREFORE, DANTRIUM SHOULD NOT BE USED WITHOUT APPROPRIATE EVALUATION AND MONITORING OF HEPATIC FUNCTION BEFORE AND THROUGHOUT TREATMENT, INCLUDING FREQUENT DETERMINATIONS OF SERUM LIVER ENZYMES. A TRIAL ADMINISTRATION OF DANTRIUM IS RECOMMENDED AND IF AFTER 45 DAYS NO OBSERVABLE BENEFIT IS EVIDENT, DANTRIUM SHOULD BE DISCONTINUED. THE LOWEST POSSIBLE EFFECTIVE DOSE FOR THE INDIVIDUAL PATIENT SHOULD BE PRESCRIBED.

TOXICITY STUDIES IN ANIMALS PROVIDED EVIDENCE OF LOW-GRADE CARCINOGENIC ACTIVITY OF DANTRIUM IN THE RAT (SEE SECTION ON TOXICOLOGY). IN VIEW OF THE ANIMAL FINDINGS, POTENTIAL CARCINOGENICITY IN HUMANS CANNOT BE DISREGARDED. THEREFORE, THE POTENTIAL BENEFITS OF THE DRUG SHOULD BE WEIGHED AGAINST THE POSSIBLE RISKS OF DRUG USE FOR THE INDIVIDUAL PATIENT. CONSIDERATION SHOULD BE GIVEN AS TO WHETHER THE PATIENT HAS RESPONDED TO OTHER MEDICATION AND TO THE BENEFITS OF THE TRIAL ADMINISTRATION OF DANTRIUM AS RECOMMENDED ABOVE. IN ASSESSING RISK ACCEPTABILITY, THE AGE OF THE PATIENT, THE DEGREE OF DISABILITY AND LIFE EXPECTANCY SHOULD ALSO BE CONSIDERED. LONG TERM EFFICACY AND OTHER ASPECTS OF THE LONG TERM SAFETY OF DANTRIUM HAVE NOT YET BEEN ESTABLISHED.

**Use in Children:** In view of the preceding warning, it is particularly important to assess risk acceptability before Dantrium is used in pediatric patients. Since there is insufficient experience with the use of Dantrium in young children (under 5 years of age), the drug is usually not recommended in this age group.

**Use in Pregnancy:** The safety of Dantrium in women who are or who may become pregnant has not been established; in such patients it should be given only when the potential benefits have been weighed against possible hazard to mother and child. Dantrium should not be used in nursing mothers.

## PRECAUTIONS

Although subjective weakness attributable to Dantrium is usually transient, some patients feel excessively weak as long as Dantrium therapy is continued. Such patients may not be able to manipulate rehabilitation devices such as wheelchairs, crutches, braces, walkers, or canes. Careful attention should be given to patients utilizing these devices. Dantrium should be discontinued if the weakness persists and interferes with the use of a rehabilitation device.

Dantrium should be used with caution in patients with impaired myocardial function.

Patients should be instructed not to drive a motor vehicle or participate in a hazardous occupation during the first week of Dantrium therapy. Although the primary pharmacologic effect of Dantrium is exerted directly on skeletal muscle, an apparent transient CNS effect also may exist. Therefore, caution should be exercised in the concomitant administration of tranquilizing agents.

Although photosensitization has not been a problem in clinical trials of Dantrium it is possible that in some subjects the drug might evoke a phototoxic response.

The possibility of cross-sensitivity with compounds of related chemical structure exists; however, no such reactions were reported in extensive clinical trials.

In long-term therapy, periodic clinical laboratory evaluation of organ systems, including haematopoietic, renal, and hepatic studies, should be performed.

## ADVERSE REACTIONS

Side effects most frequently reported were drowsiness, weakness, dizziness, malaise, fatigue and diarrhea. Less commonly reported effects are listed by systems.

**Cardiovascular:** tachycardia and erratic blood pressures, phlebitis.

**Gastrointestinal:** constipation, anorexia, gastric irritation and bleeding, abdominal cramps, swallowing difficulty, nausea with or without vomiting and liver failure.

**CNS:** speech and visual disturbances, seizure, headache, lightheadedness, taste alterations, mental depression, confusion, nervousness, diplopia, insomnia.

**Urogenital:** increased urinary frequency, crystalluria, difficult erection, urinary incontinence and/or nocturia, difficult urination and/or urinary retention.

**Musculoskeletal:** myalgia, backache.

**Integumentary:** acne-like rash, pruritis, urticaria, eczematoid eruption, abnormal hair growth, sweating.

**Other:** chills, fever, excessive tearing, feeling of suffocation.

ALTERATIONS OF LIVER FUNCTION STUDIES ATTRIBUTABLE TO DANTRIUM HAVE BEEN OBSERVED. IT IS THEREFORE ADVISABLE TO PERFORM LIVER FUNCTION TESTS BEFORE AND DURING THERAPY. (SEE WARNINGS).

Side effects listed as most frequently occurring were generally transient and may be avoided with initial low doses and a gradual increase to optimal doses. Diarrhea may be of sufficient severity to warrant temporary or possibly permanent withdrawal of medication.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

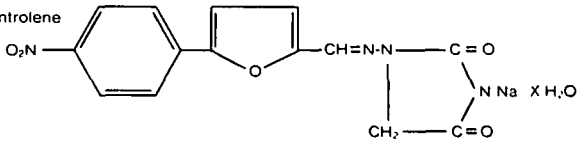
A single case has been reported of a patient with an 18-year history of multiple sclerosis who consumed 1600 mg of Dantrium per day for 13 days (a total of 20,800 mg). Other than feeling slightly weaker and "rubbery", the patient appeared to suffer no clinical manifestations of overdosage. Liver function values were transiently elevated although the patient did not become jaundiced.

For acute overdosage general supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystalluria. An adequate airway should be maintained and artificial resuscitation equipment made available. Electrocardiographic monitoring should be instituted, and the patient carefully observed. No experience has been reported with dialysis, hence its value in Dantrium overdosage is not known.

## PHARMACOLOGY

Chemical Name: 1-[5-(p-nitrophenyl)-furfurylidene]amino hydantoin sodium hydrate

Sodium Dantrolene




Dantrium causes marked, dose-dependent skeletal muscle relaxation in laboratory animals with a long duration of action. The pharmacologic profile of Dantrium in animals is unlike neuromuscular blocking agents in that total muscle paralysis and/or respiratory depression do not occur.

There is a wider margin between doses causing muscle relaxation and doses causing motor incoordination with Dantrium than with centrally acting muscle relaxants. Skeletal muscle relaxation is not associated with anaesthetic or analgesic action. Impairment of cornea or pinna reflexes has not been observed in animals treated with Dantrium.

Various studies both in vivo and in vitro demonstrated the apparent selectivity of action of Dantrium for skeletal muscle. There were some non-specific depressant effects seen in several smooth muscle studies and insignificant effects in cardiac muscle in doses which cause skeletal muscle relaxation. Nerve transmission was not affected by Dantrium in several animal studies.

It has been shown that Dantrium has no effect on the propagated action potential recorded on the muscle membrane, and the total membrane capacitance is not decreased by the drug, indicating that it does not disrupt the function of the transverse tubular system, and acts at a point beyond the electrically excitable surface membrane. Evidence obtained in vitro with muscle preparations exposed to caffeine, an agent known to cause muscle contractions by releasing internal $Ca^{++}$ stores in muscle, suggests that Dantrium acts on skeletal muscle by altering the $Ca^{++}$ release mechanisms. Such an action could explain the apparent specificity of Dantrium for skeletal muscle.

Animal studies have indicated that Dantrium is metabolized by hydrolysis, hydroxylation, nitro reduction and acetylation of the resulting amine.

Four corresponding metabolites have been identified which probably do not contribute significantly to the activity of Dantrium. Maximal blood levels following oral administration are reached in approximately 1 hour. In dogs approximately 40% of an I.V. dose of Dantrium is excreted as the hydroxylated metabolite in bile whereas only 1% of the dose is excreted in this manner by the rat. High biliary concentrations of this metabolite have also been found in the Rhesus monkey. Total excretion of known metabolites in the urine is estimated at approximately 3% in the dog and approximately 10% in the rat.

## TOXICOLOGY

The oral $LD_{50}$ of dantrolene sodium in newborn Sprague-Dawley rats was 2902 mg/kg. No young adult rats were killed with doses up to 18,000 mg/kg. Pertinent clinical signs were inactivity, lethargy, weakness, gasping, diarrhea, yellowing of skin colour, decreased growth rate or weight loss, and death. Tubular degeneration and necrosis, cortical abscesses and pelvic necrosis occurred in kidneys. No deaths occurred within 48 hours in adult rabbits and mice, with oral doses up to 8 or 9 g/kg, respectively. Crystals were observed in the urinary and the gall bladders of rabbits.

Three subacute toxicity studies were conducted in rats with oral doses up to 500 mg of dantrolene sodium/kg for 28 days and up to 86 mg/kg for 88 days. Body weight gains were reduced significantly by doses of 43.8 mg/kg. Relative kidney and liver weights were increased by doses of 15.5 mg/kg and absolute liver weights by 86 mg/kg for 88 days. Increased serum alkaline phosphatase and SGOT occurred with doses of 62.5 mg/kg. Rats dosed with 500 mg/kg for 28 days had increased serum alkaline phosphatase, SGOT, fasting plasma glucose, plasma urea nitrogen, serum creatinine, and decreased urine specific gravity. Renal tubules were plugged by drug crystals and tubular dilatation, degeneration, necrosis and hematuria resulted.

Chronic toxicity studies were conducted in Beagle dogs for 1 year. Oral doses of 15 mg/kg/day produced no detectable effects. At 30 mg/kg/day, there was a suppresion of weight gain and sporadic increases in BSP retention. A regimen of increasing doses (90 mg/kg for the first 206 days followed by 180 mg/kg for 14 days and 360 mg/kg for an additional 82 days) caused marked loss in body weight, increased SGOT activity and BSP retention, normocytic orthochromic anaemia, urinary anisotropic crystals and, in one dog necropsied at day 270, intrahepatic cholestasis. Recovery occurred after discontinuation of drug administration.

A one-year oral toxicity study also was conducted with Rhesus monkeys. Initial doses of 0, 15, 30 and 60 mg/kg were used. Because of the lack of clinical toxicity during the first 6 months, the dosage levels were doubled at the end of the first 6 months. At 9 months, the dosage level for the high dose group was again doubled and these animals were then maintained on 240 mg/kg/day until the termination of the study. A dose-dependent lowering of body weight gain was observed at 12 months. Urinary crystals were noted in one animal at the middle (60 mg/kg/day) dosage level at 11½ to 12 months. Urinalyses at 6 and 12 months also indicated a drug-related increase in blood elements. During the last 6 months, a generally lower A/G ratio at all dosage levels, a slight, apparently dose-related cholesterol-lowering effect, a higher serum alkaline phosphatase, a high SGOT level in the two high dosage levels and relatively lower serum creatinine levels in the high dosage groups were noted. Chronic hepatic cholangitis was observed at necropsy in some mid and high dosage level animals.

Dantrolene sodium was administered in the diet to mature Sprague-Dawley rats for 18 months at levels of 15, 30 and 60 mg/kg daily. Treated rats showed a lower body weight gain compared to controls and damage to the liver. There was an increase in the incidence of mammary adenofibromas in the females. Other drug-related changes (seen only at the 30 and 60 mg/kg daily dosage levels) were increased incidences of bile duct cystadenomas, and increased signs of malignancy in mammary tumors in females. At the 60 mg/kg daily level the number of metastasizing mammary adenocarcinomas in female rats was increased significantly; anisotropic urinary crystals were found in both male and female groups.

Because of these findings, lifetime tumorigenesis studies were conducted in Sprague-Dawley and Fischer 344 rats. The treated Sprague-Dawley rats received dantrolene sodium in the diet at levels of 15, 30 and 60 mg/kg daily for 18 months and the Fischer 344 rats received the same levels for 20 months. The animals subsequently were maintained on a standard diet until 90% of each treatment group died spontaneously. Dantrium produced in the female Sprague-Dawley rats a linear, dose-related increase in the number of rats with malignant neoplasms, and a decrease in the time of onset of mammary neoplasms. There were also increased incidences of benign hepatic tumors including lymphangiomas and bile duct cystadenomas, and angiosarcomas. In Fischer rats, there was a significant, dose-related reduction in the times of onset of mammary and testicular tumors.

A two year tumorigenesis study was conducted in Swiss mice (CD®-1 HaM ICR). Dantrolene sodium was fed to mice at levels of 15, 30 and 60 mg/kg/day for 15 months and then the mice were maintained on a standard diet for 9 additional months. There was an increased incidence of benign angiomatous neoplasms.

**Effects on Reproduction:** Dietary doses of 0, 15 or 45 mg of dantrolene sodium/kg of body weight were given to rats and rabbits in classical reproductive and teratogenic studies. Significant untoward effects were not observed. One litter of 14 pups from a rat treated with 45 mg of dantrolene sodium/kg between days 6 to 15 of gestation had 6 malformed pups. Malformations included kinky tails, a short upper jaw, and renal agenesis. Two pups in another litter had unilateral microphthalmia. An association with treatment was considered doubtful.

## DOSAGE AND ADMINISTRATION

Prior to the administration of Dantrium, consideration should be given to the potential response to treatment. A decrease in spasticity sufficient to allow a daily function not otherwise attainable should be the therapeutic goal of treatment with Dantrium. Refer to section on "Clinical Uses" for description of possible areas of response.

It is important to establish a therapeutic goal (regain and maintain a specific function such as therapeutic exercise program, utilization of braces, transfer manoeuvres etc.) before beginning Dantrium therapy. Dosage should be increased until the maximum performance compatible with the dysfunction due to underlying disease is achieved. No further increase in dosage is then indicated.

**Usual Dosage:** It is important that the dosage be titrated and individualized for maximum effect. The lowest dose compatible with optimal response is recommended.

**Adults:** Begin therapy with 25 mg once daily, increase to 25 mg two, three or four times daily and then by increments of 25 mg to 100 mg two, three, or four times daily if necessary. Each dosage level should be maintained for four to seven days, depending on the patient's tolerance, and should be increased only if the therapeutic goal has not been attained. Only occasionally will a dose greater than 100 mg four times daily be required in which case the dose can be increased gradually, depending on tolerance, up to 200 mg four times daily.

The dose should not be increased beyond, and may even have to be reduced to, the amount at which the patient received maximal benefit without adverse effects.

**Children:** A similar approach should be utilized, starting with 1.0 mg/kg of body weight once daily, this is increased to 1.0 mg/kg two, three, or four times daily and then, by increments of 0.5 mg/kg, up to 3.0 mg/kg two, three, or four times daily if necessary. Each dosage level should be maintained for four to seven days depending on the patient's tolerance, and should be increased only if the therapeutic goal has not been attained. Doses higher than 100 mg four times daily should not be used in children.

## DOSAGE FORMS

Dantrium is available in opaque orange and brown capsules of 25 mg (coded "Eaton 030" in black), and opaque orange and brown capsules of 100 mg (coded "Eaton 033" in white). They are supplied in bottles containing 100 and 500 capsules.

Dantrium is a registered trademark.

Norwich-Eaton Pharmaceuticals
Division of Norwich-Eaton Ltd.
P.O. Box 2002
Paris, Ontario
N3L 3G6

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# *DILANTIN/ ZARONTIN*

## BRIEF PRESCRIBING INFORMATION

**INDICATIONS (DILANTIN):**

DILANTIN is indicated for the control of grand mal epilepsy, psychomotor seizures, and certain other convulsive disorders. Parenteral DILANTIN is indicated for the treatment of status epilepticus and the prophylactic control of seizures in neurosurgery.

**PRECAUTIONS AND CONTRAINDICATIONS (DILANTIN):**

Periodic examination of the blood is advisable since hematologic disorders in association with DILANTIN administration have been reported. Nystagmus in combination with diplopia and ataxia indicates dosage should be reduced. When DILANTIN with PHENOBARBITAL or PHELANTIN are used, it should be borne in mind that phenobarbital may cause drowsiness, and may be habit-forming. PHELANTIN, because of the methamphetamine content, should be given cautiously to patients with hypertension.

PHELANTIN is contraindicated in patients hypersensitive to ephedrine-like compounds; in those showing anxiety or undue excitability; and in patients with cardiac or coronary disease not likely to tolerate vasoconstrictors. The possibility of toxic effects of DILANTIN during pregnancy has not been explored.

**ADVERSE REACTIONS (DILANTIN):**

Once proper dosage has been determined, toxic effects of DILANTIN are infrequent. Minor side effects which may occur during the initial stages of therapy include gastric distress, nausea, weight loss, transient nervousness, sleeplessness, and a feeling of unsteadiness, all of which usually subside with continued use. Allergic phenomena such as polyarthropathy, fever, and skin eruptions may occur. Acute generalised morbilliform eruptions with or without a temperature elevation, may occur about two weeks after treatment is begun. The dermatitis may in some instances go on to exfoliation and hepatitis may occur, contraindicating further therapy with DILANTIN. Eruptions usually subside when therapy is discontinued.

Gingival hypertrophy, hirsutism, and excessive motor activity are occasionally encountered, especially in children, adolescents, and young adults. Only occasionally is it necessary to discontinue DILANTIN because of these manifestations. Gingival hypertrophy can be greatly minimized by scrupulous daily care of gums and prophylactic dental care.

Megaloblastic anemia and macrocytosis have been reported but have responded to antianemic therapy. Leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia, and agranulocytosis have also been reported. Usually these patients were simultaneously receiving other drugs. Lupus erythematosus and erythema multiforme have occurred in patients receiving DILANTIN.

**DOSAGE AND ADMINISTRATION (DILANTIN):**

In all cases, optimal dosage of DILANTIN must be determined by trial. Dosage in excess of the minimum required to prevent convulsions is not recommended. For most patients, DILANTIN CAPSULES, 100 mg or DILANTIN CAPSULES, 30 mg are suitable for administration.

**FORMS AVAILABLE:**

In order to provide versatile therapy, DILANTIN is supplied in the following convenient product forms:

DILANTIN® CAPSULES, 100 mg (Cap 362). Each white capsule with orange cap contains phenytoin sodium 100 mg.

DILANTIN® CAPSULES, 30 mg (Cap 365). Each white capsule with pale pink cap contains phenytoin sodium 30 mg.

DILANTIN® INFATABS, 50 mg. Each triangular shaped, grooved tablet, contains 50 mg phenytoin.

INFATABS are palatably flavoured tablets, intended primarily for pediatric use.

DILANTIN-125 SUSPENSION. Each 5 ml contains 125 mg phenytoin. DILANTIN-30 SUSPENSION. Each 5 ml contains 30 mg phenytoin.

These are pleasantly flavoured suspensions of DILANTIN, especially adapted for pediatric use, but suitable for adolescents and adults who prefer liquid medication.

℗ DILANTIN® with 15 mg PHENOBARBITAL CAPSULES, (Cap. 375). Each white capsule with garnet cap contains 100 mg phenytoin sodium and 15 mg phenobarbital.

℗ DILANTIN with 30 mg PHENOBARBITAL CAPSULES (Cap. 531). Each white capsule with black cap contains 100 mg phenytoin sodium and 30 mg phenobarbital.

These combinations of DILANTIN with PHENOBARBITAL are supplied for the convenient and economical use of those patients who require combined DILANTIN and PHENOBARBITAL therapy.

℗ PHELANTIN CAPSULES®, (Cap. 394). Each yellow capsule contains phenytoin sodium, 100 mg; phenobarbital. 30 mg; and methamphetamine hydrochloride, 2.5 mg.

Combining these agents takes advantage of the clinically proved anticonvulsant actions of DILANTIN and phenobarbital, while the methamphetamine counteracts the sedative effects of phenobarbital.

DILANTIN® AMPOULES, 100 mg (Amp. 1488). Each 2 ml ampoule contains 100 mg (50 mg/ml) phenytoin sodium ready-mixed.

DILANTIN® AMPOULES, 250 mg (Amp. 1475). Each 5 ml ampoule contains 250 mg (50 mg/ml) of phenytoin sodium ready-mixed.

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**INDICATIONS (ZARONTIN):**

ZARONTIN is indicated for the control of petit mal epilepsy.

**PRECAUTIONS (ZARONTIN):**

The physician should be alert to any symptoms indicative of the following conditions which have been reported in association with the use of ZARONTIN: aplastic anemia, agranulocytosis, dermatitis, leukopenia. Periodic blood counts should be performed. The drug should be used with caution in patients with known liver or renal disease or dysfunction. Routine urinalyses and frequent liver function tests are advised. Safe use of this drug in pregnancy has not been established.

Because of the possibility of drug-induced drowsiness, operation of motor vehicles or other machinery by patients on ethosuximide therapy is not advised. ZARONTIN when used alone in mixed types of epilepsy may increase the frequency of grand mal attacks in some patients.

**ADVERSE REACTIONS (ZARONTIN):**

In 727 patients gastrointestinal side effects occurred in 12.5%, central nervous system symptoms in 6.7%, blood changes in 0.4%, and miscellaneous side effects in 1.2%. Side effects are usually mild and transient and usually subside with continued therapy. Anorexia, gastric distress, nausea, emesis, drowsiness, headache, dizziness, euphoria, and singultus have been reported. Psychiatric or psychologic aberrations, including insomnia, night terrors, inability to concentrate, motor unrest, agitation, and aggressiveness thought to be drug-induced or exacerbated by anticonvulsant medication, were noted in a few patients who had previously shown emotional instability. Leukopenia, agranulocytosis, and severe pancytopenia with fatal outcome, have been reported in association with ethosuximide. In most cases of leukopenia, the condition cleared either on reduction of dosage or discontinuation of the drug. Other reactions in which the extent of ethosuximide implication is not yet determined include myopia, rash, vaginal bleeding, swelling of the tongue, and hirsutism. One instance of temporarily elevated (3-plus) cephalin flocculation test has been reported; patient showed normal values as medication continued.

**DOSAGE AND ADMINISTRATION (ZARONTIN):**

The initial dose for children under six years of age is 250 mg (1 capsule or 5 ml of syrup) per day; for patients six years of age and older, 500 mg (2 capsules or 10 ml of syrup) per day. The dose thereafter must be individualized according to the patient's response.

**FORMS AVAILABLE:**

ZARONTIN® CAPSULES, 250 mg (Cap. 237). Each soluble gelatin capsule contains 250 mg ethosuximide.

ZARONTIN® SYRUP: Each 5 ml contains 250 mg ethosuximide.

Full prescribing information available on request.

**PARKE-DAVIS**

PMAC

Parke, Davis & Company, Ltd.
Scarborough, Ont. M1K 5C5

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**Brief Prescribing Information**
**Tegretol® 200 mg** carbamazepine

**Indications and Clinical Use**

A. *Trigeminal Neuralgia:*
Tegretol 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:*
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 essentially ineffective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge.

**Contraindications**
Tegretol 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.
Safe use in pregnancy has not been established. Therefore, Tegretol should not be administered during the first three months of pregnancy. 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 (See Reproductive Studies). Because of demonstrated toxicity in nursing animals, Tegretol should not be administered to nursing mothers.
Because of the similarity of chemical structure, Tegretol should not be administered to patients with known hypersensitivity to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites.

**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.**

**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. 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 should be immediately discontinued until the case is carefully reassessed.
*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 E.K.G. should be performed before administering Tegretol, in order to exclude patients with atrioventricular block.
*Use in Patients taking Oral Contraceptives:* In women under treatment with Tegretol, the reliability of oral contraceptives may be adversely affected; such patients should accordingly be advised to use some alternative, non-hormonal method of contraception.
*Driving and operating Hazardous Machinery:* Because dizziness and drowsiness are possible side effects of Tegretol, patients shoud be warned about the possible hazards of operating machinery or driving automobiles.

**Adverse Reactions**
The reactions which have been most frequently reported with Tegretol 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 haematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.
The following adverse reactions have been reported:
*Haematological reactions:* Transitory leucopenia, eosinophilia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.
*Hepatic disturbances:* During the long-term administration of Tegretol, abnormalities in liver function tests and cholestatic or hepatocellular jaundice have been observed.
*Dermatological reactions:* 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, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus erythematosus.
*Neurological reactions:* The reactions reported as occurring during treatment with Tegretol include vertigo, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, 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, 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 systems:* Recurrence of thrombophlebitis in patients with a prior history 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, and impotence. Elevation of BUN, albuminuria and glycosuria also have been observed.
*Digestive tract:* Disturbances associated with Tegretol therapy have included nausea, vomiting, gastric or abdominal discomfort, diarrhoea, anorexia and 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 analogy, periodic eye examinations, including slitlamp fundoscopy and tonometry, are recommended.
Other reactions reported during treatment with Tegretol include fever and chills, lymphadenopathy, aching joints and muscles, leg cramps and conjunctivitis.

**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 depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, until the best response is obtained, up to 600 mg daily. The usual optimal dosage is 600 mg daily, but occasionally dosages 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 in reached.
*Use in-trigeminal neuralgia:* The initial daily dosage should be small; 200 mg, taken in two doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg per day until relief of pain is obtained. This is usually achieved at a dosage between 200 and 800 mg daily, but occasionally up to 1200 mg per day 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 of the drug in trigeminal neuralgia is not recommeded.
Tegretol should be taken in two or three divided doses daily, with meals whenever possible.

**Dosage Forms**
Tegretol is available as a 200 mg white, round, flat, bevelled-edged, double-scored tablet, imprinted with the GEIGY monogram.

**Availability**
Bottles of 50 and 500 tablets. Protect from heat and humidity.

Full information available on request.

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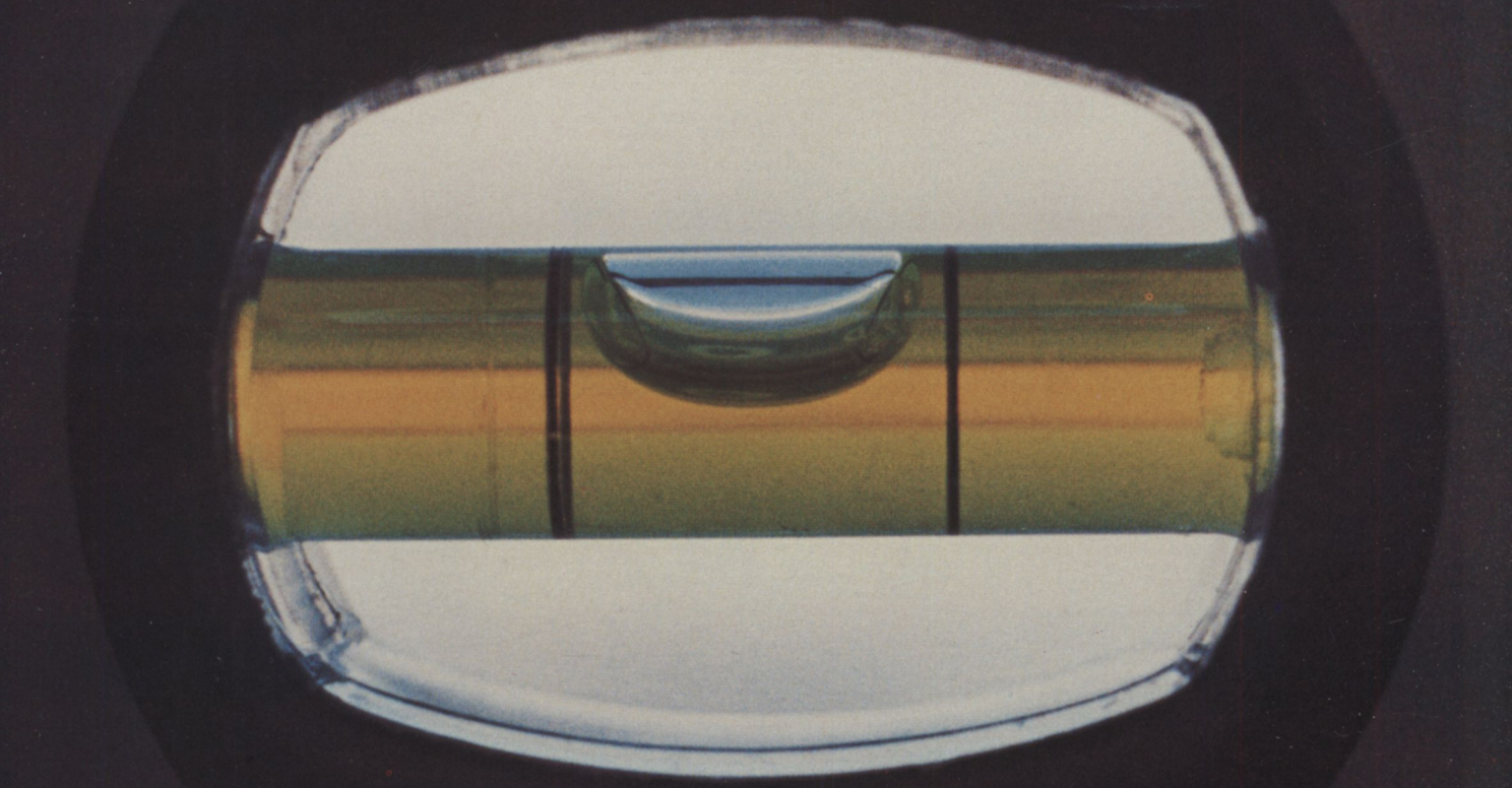
**Geigy**
Dorval, Qué. H9S 1B1 G-9091

# Sinemet*

(levodopa and carbidopa combination)



## Helps restore the equilibrium of dopamine/acetylcholine in the parkinsonian patient by efficiently increasing the cerebral supply of dopamine

In most patients

SINEMET* permits control of the major symptoms particularly rigidity and bradykinesia, and helps reduce or eliminate peripheral levodopa side effects. Thus, SINEMET* enables patients to lead more productive lives.

SINEMET* offers prompt therapeutic response—optimum dosage can usually be achieved within 2-3 weeks.

## To bring the world of the parkinsonian patient back into balance

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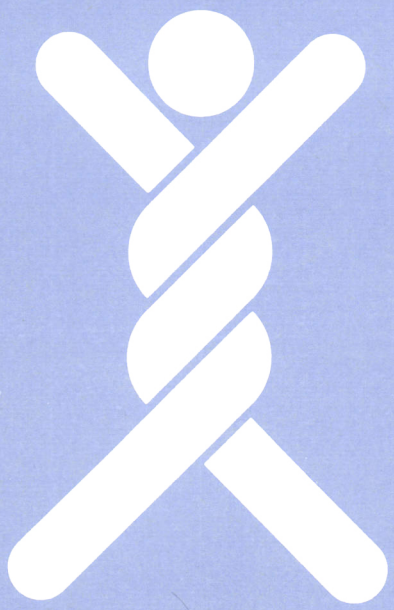
# New Lior

baclofen

## for spasticity resulting from multiple sclerosis, spinal cord injury, and spinal cord diseases.



### Acts primarily at the spinal level

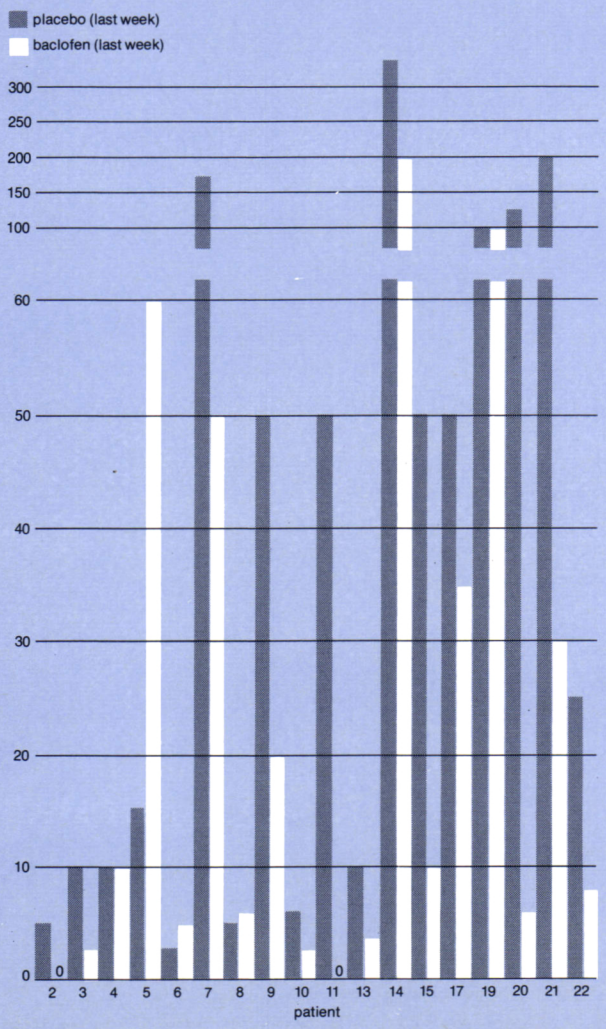
Lioresal is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of the afferent terminals. However, the precise mechanism of action is not fully known. Actions at supraspinal sites may also occur and contribute to the clinical effect.

# esal®

## Effective and safe

Results of a four-week, double blind crossover study of 22 patients showed 72 percent of 18 patients with spontaneous daytime spasms had a reduction in the frequency when treated with Lioresal. Furthermore, a reduction in severity amplitude, and duration of remaining spasms was also reported in patients treated with Lioresal.[1]

Figure 1. Average daily number of spasms during the last week of baclofen and placebo treatment periods in the 18 patients with spontaneous daytime spasms. (From Duncan et al[1])




When compared with placebo and diazepam in a double-blind study, Lioresal proved to be effective in reducing the number of spasms in 50% of patients who had developed tolerance to diazepam.[2]

In one study of 14 patients with spasticity, "Baclofen caused less sedation than would have been expected from comparable doses of diazepam but it did nevertheless have a tranquilizing effect..."[3]

And in one double-blind study, "No serious side effects developed and there were no signs of even transient bone marrow, liver, kidney, or gastrointestinal toxicity."[1] A few cases of increased SGOT, elevated alkaline phosphatase and elevated blood sugar have been reported but are not clinically significant. Gastrointestinal and other side effects also have been reported but generally do not persist.

## Facilitates physical therapy

By relieving painful spasms Lioresal may allow more active physical therapy and daily function.

The advantages of improvement in resistance to passive movement noted in patients treated with Lioresal included more comfortable positioning and easier transfers and nursing.[1]

Effect of treatment on resistance to passive movement (Adapted from Duncan et al[1])

| Stage | Baclofen | Placebo |
|---|---|---|
| **Improved** | 11 **(55%)** | 1 **(5%)** |
| **Worsened** | 0 **(0%)** | 0 **(0%)** |
| **Unchanged** | 9 **(45%)** | 19 **(95%)** |
| Total | 20 | 20 |

Geigy

For Brief Prescribing Information, see over

G-9038

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# EPILEPSY:

## Neurotransmitter, Behaviour and Pregnancy

Joint publication of
CANADIAN LEAGUE AGAINST EPILEPSY
WESTERN INSTITUTE ON EPILEPSY
1979

CONTENTS



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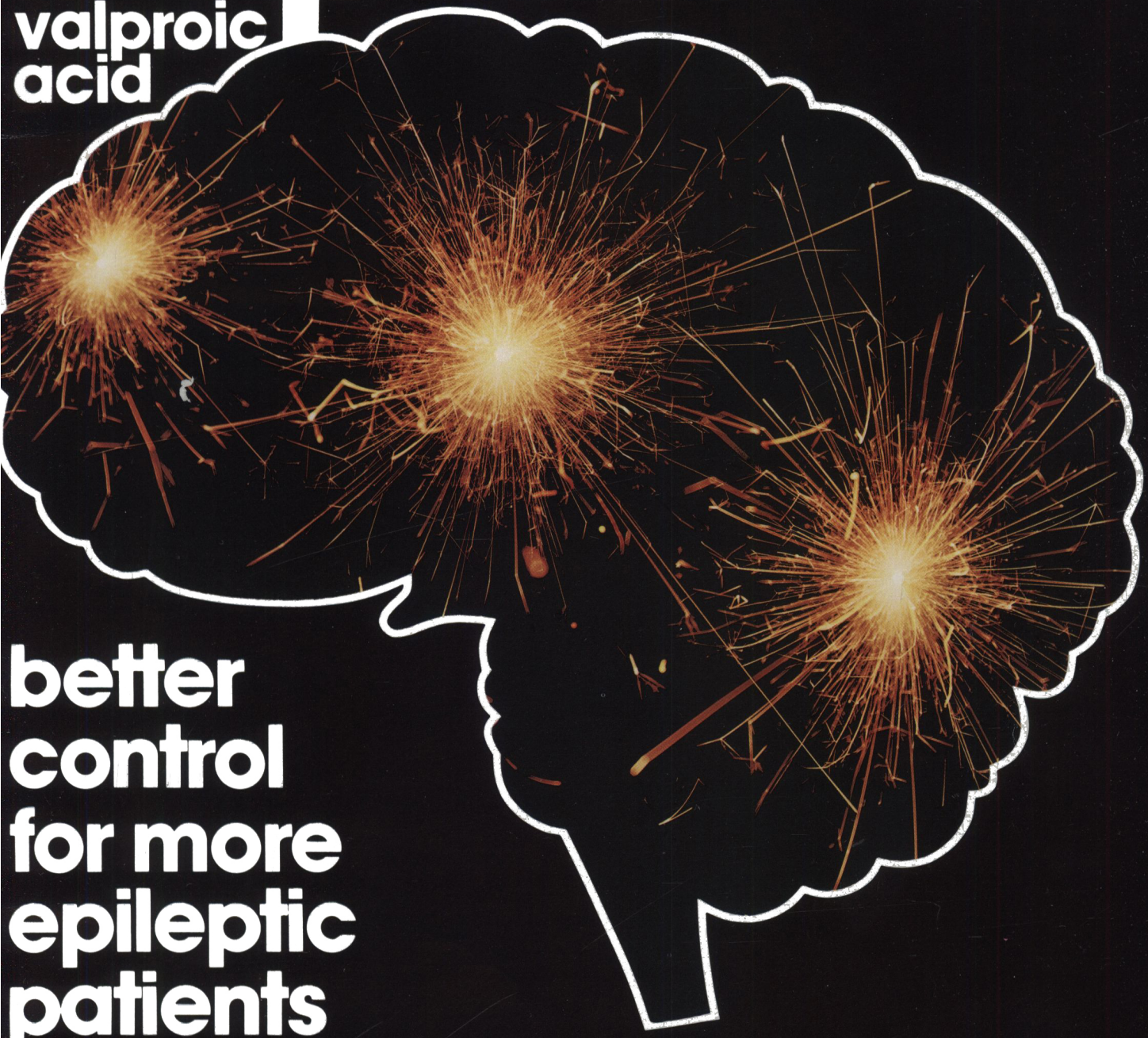
# Depakene*

valproic acid



better control for more epileptic patients

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# Depa

## valproic acid

A major advance in anti-convulsant therapy that could bring more epileptic patients closer to normal.
as sole and adjunctive treatment of simple or complex absence seizures, including petit mal.
as adjunctive therapy of multiple seizures that include absence attacks.

## a unique chemical structure

DEPAKENE is a simple fatty acid, chemically unrelated to other anticonvulsants.




## a physiological mode of action

DEPAKENE appears to increase GABA ($\gamma$-aminobutyric acid) levels in the brain and cerebellum. GABA is known to inhibit neuronal excitability.[1]

# Depakene extends the range

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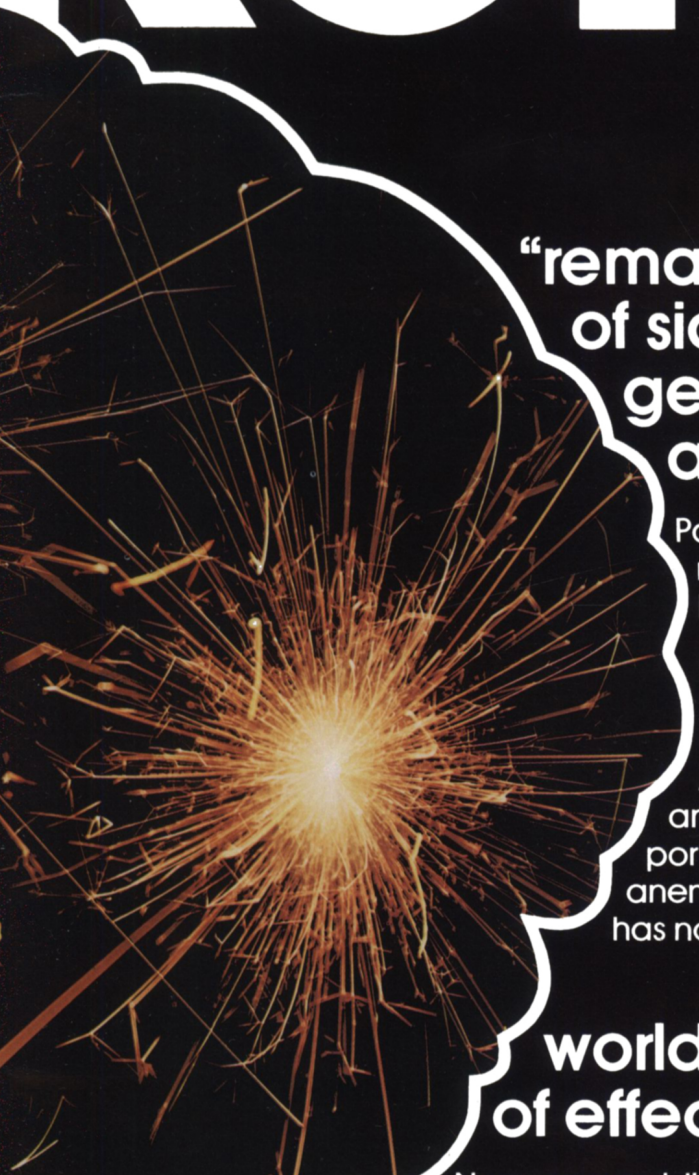
# kene



## "remarkably free of side effects in the general context of antiepileptics"[3]

Patients taking DEPAKENE have been reported to be more lively and alert and better able to carry out their daily tasks.[3]

DEPAKENE has not been associated with cosmetically undesirable side effects such as hirsutism, acne and gum hyperplasia. Although inhibition of platelet aggregation and leukopenia have been occasionally reported, it has not been associated with aplastic anemia or agranulocytosis. And DEPAKENE has no record of tolerance in long-term use.[2]

## world-wide documentation of effectiveness

Numerous publications and clinical trials involving more than 4000 patients whose ages ranged from 5 months to 71 years, have demonstrated the antiepileptic efficacy of DEPAKENE.

An overview of clinical studies[2] involving valproic acid in 1020 patients demonstrates an excellent (75-100%) reduction in seizure frequency in 45.7% of patients, and satisfactory results (33-74% reduction of seizures) in 25.4% more.

# of anticonvulsant therapy.

# Depakene
valproic acid

## Prescribing Information

### CLINICAL PHARMACOLOGY

Depakene (valproic acid) has anticonvulsant properties. 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).

Valproic acid is rapidly absorbed after oral administration. Peak serum levels occur approximately one to four hours after a single oral dose. The serum half-life ($t_{0.5}$) of valproic acid is approximately 8 to 12 hours. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. The therapeutic plasma concentration range is believed to be from 43 to 86 μg/mL.

Excretion 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.

### INDICATIONS AND CLINICAL USE

Depakene (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple seizure types which include absence.

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

Depakene (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

### WARNINGS

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in a few patients receiving Depakene (valproic acid) and concomitant anticonvulsant drugs. These events have occurred during the first six months of treatment with valproic acid. Although a causal relationship has not been established, caution should be observed when administering Depakene to patients with pre-existing liver disease. Liver function tests should be performed prior to therapy and every two months thereafter.

#### Use in pregnancy

The safety of Depakene (valproic acid) during pregnancy has not been established, however, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks in treating or counselling women of childbearing age who have epilepsy.

Recent reports indicate an association between the use of anticonvulsant 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 two to threefold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. 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.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk 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 antiepileptic medication is in doubt, appropriate consultation might be indicated.

#### Nursing Mothers

Depakene is secreted in breast milk. As a general rule, nursing should not be undertaken while a patient is receiving Depakene.

#### Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 350 mg/kg/day in rats and 90 mg/kg/day in dogs. The effect of Depakene (valproic acid) on the development of the testis and on sperm production and fertility in humans is unknown.

### PRECAUTIONS

#### General

Because of rare reports of platelet aggregation dysfunction, thrombocytopenia and elevated liver enzymes, it is recommended that liver function tests, platelet counts and bleeding time determinations be performed before initiation of therapy and at periodic intervals.

Because valproic acid may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see Drug Interactions).

Valproic acid is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

#### Driving and Hazardous Occupations

Valproic acid 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

**Depakene (valproic acid) may potentiate the CNS depressant action of alcohol.**

**There is evidence that valproic acid may cause an increase in serum phenobarbital levels, although the mechanism is unknown. 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.**

**There is conflicting evidence regarding the interaction of valproic acid with phenytoin. It is not known if there is a change in unbound (free) phenytoin serum levels. The dose 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 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 Depakene (valproic acid) has usually been used with other anticonvulsants, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

#### Gastrointestinal

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

#### CNS Effects

Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anticonvulsant 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 who were also on phenobarbital.

#### Dermatologic

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

#### Psychiatric

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

#### Musculoskeletal

Weakness has been reported.

#### Hematopoietic

Valproic acid inhibits the secondary phase of platelet aggregation. This may be reflected in altered bleeding time. Relative lymphocytosis and mild thrombocytopenia have also been noted in isolated cases. Leukopenia has been reported.

#### Hepatic

Increases in serum alkaline phosphatase and serum glutamic oxaloacetic transaminase have been noted. Isolated cases of severe hepatotoxicity have been reported (see Warnings).

### SYMPTOMS AND TREATMENT OF OVERDOSAGE

In a reported case of overdosage with Depakene (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.

As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

### DOSAGE AND ADMINISTRATION

Depakene (valproic acid) is administered orally. The recommended initial dose 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 maximum recommended dose is 30 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen.

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

| Weight | | Total Daily Dose (mg) | Number of Capsules or Teaspoonsful of Syrup | | |
|---|---|---|---|---|---|
| kg | lb | | Dose 1 | Dose 2 | Dose 3 |
| 10-24.9 | 22-54.9 | 250 | 0 | 0 | 1 |
| 25-39.9 | 55-87.9 | 500 | 1 | 0 | 1 |
| 40-59.9 | 88-131.9 | 750 | 1 | 1 | 1 |
| 60-74.9 | 132-164.9 | 1,000 | 1 | 1 | 2 |
| 75-89.9 | 165-197.9 | 1,250 | 2 | 1 | 2 |

As the dosage of valproic acid is raised, blood levels of phenobarbital and/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 should be swallowed without chewing to avoid local irritation of the mouth and throat.

### AVAILABILITY

Depakene (valproic acid) is available as orange-coloured, soft-gelatin capsules of 250 mg in bottles of 100 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. Depakene is a prescription drug (Schedule F).

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3. Pinder, R.M. et al., Sodium valproate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Epilepsy, Drugs 13, 81-123, 1977.

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## XVth Canadian Congress of Neurological Sciences,

Ottawa, Ontario

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## Thirteenth Annual Recent Advances in Neurology

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These three Societies meet together as the Canadian Congress of Neurological Sciences once a year. The meetings are usually held in the third week in June. A different city is chosen for the meeting each year.

Details regarding membership in each of the Societies, the date and place of the meeting and the scientific program can be obtained from the Secretaries.

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