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The Canadian Neurological Society
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology

XVII Canadian Congress of Neurological Sciences
Toronto, Ontario June 23 - 26, 1982

VOLUME 9, NO. 2 MAY 1982

SERC®

(betahistine hydrochloride tablets)

For the management of Vertigo

■ Proven efficacy

"(Serc) is now a proven, useful therapeutic agent in the treatment of Ménière's disease, especially in the control of vertigo."[1]

■ Restores vestibular responses

"In a preliminary trial (Wilmot 1971) using objective testing of both auditory and vestibular function,...the results showed statistical significance in favour of Serc."[2]

■ Reduced severity of episodic vertigo

"...a significant improvement in favour of the drug (Serc) with regard to vertigo, tinnitus and deafness. Vertigo was the most responsive symptom."[1]

■ Well tolerated

"No adverse reactions were observed."[1]

REFERENCES:

1Frew, I.J.C. et al: Postgrad. Med. J.; 52:501-503, 1976.

2Wilmot, T.J. et al: J. Laryng. Otol; 9:833-840, 1976.

PRESCRIBING INFORMATION

INDICATIONS: SERC may be of value in reducing the episodes of vertigo in Meniere's disease. No claim is made for the effectiveness of SERC in the symptomatic treatment of any form of vertigo other than that associated with Meniere's disease.

DOSAGE AND ADMINISTRATION: The usual adult dosage has been one to two tablets (4 mg. each) administered orally three times a day.

Recommended starting dose is two tablets three times daily. Therapy is then adjusted as needed to maintain patient response. The dosage has ranged from two tablets per day to eight tablets per day. No more than eight tablets are recommended to be taken in any one day.

SERC (betahistine hydrochloride) is not recommended for use in children. As with all drugs, SERC should be kept out of reach of children.

CONTRAINDICATIONS: Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using SERC. Although no causal relation has been established SERC is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. SERC is also contraindicated in patients with pheochromocytoma.

PRECAUTIONS: Although clinical intolerance to SERC by patients with bronchial asthma has not been demonstrated, caution should be exercised if the drug is used in these patients.

USE IN PREGNANCY: The safety of SERC in pregnancy has not been established. Therefore, its use in pregnancy or lactation, or in women of childbearing age requires that its potential benefits be weighed against the possible risks.

ADVERSE REACTIONS: Occasional patients have experienced gastric upset, nausea and headache.

HOW SUPPLIED: Scored tablets of 4 mg each in bottles of 100 tablets.

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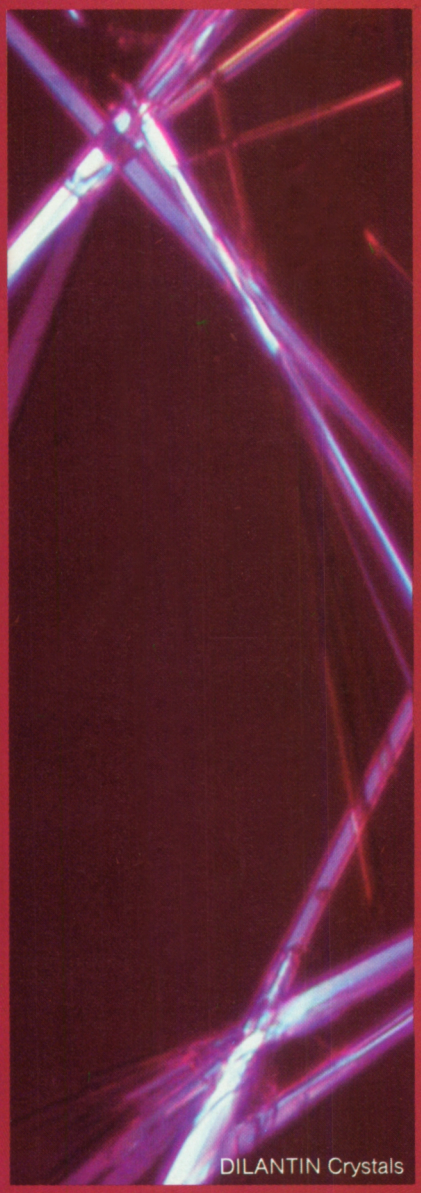
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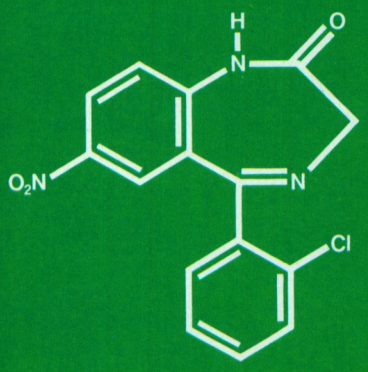

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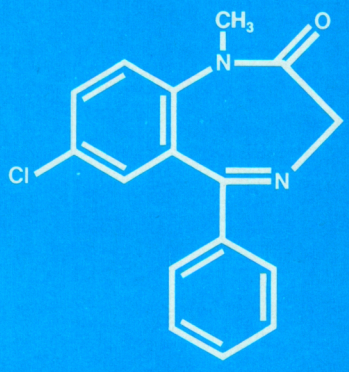

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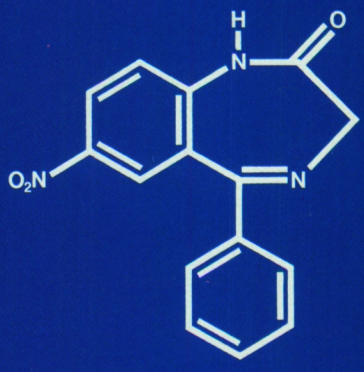

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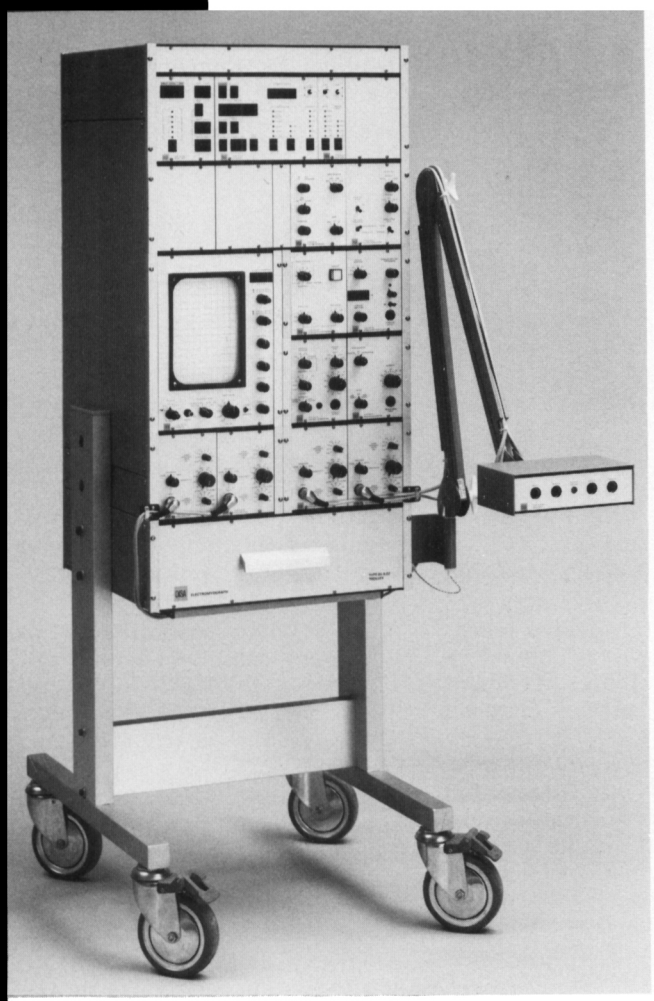

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THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES
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THE EDITORIAL BOARD wishes to publish original work in the basic and clinical neurosciences on the understanding that it has not been and will not be published elsewhere Review articles on timely subjects will be accepted. Manuscripts must be in triplicate including illustrations. One of the copies must be the original, ribbon copy. Manuscripts should be typed double spaced, on white paper.

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.

Papers should be identified only by the full name of the author, or authors, and the name of the place in which the work was done.

ILLUSTRATIONS: Photographs should be unmounted on glossy paper and show magnification scale. They should be marked on the back with figure number, title of paper and name of author.

Diagrams should be in India ink and large enough to be informative after reduction.

All illustrations should be referred to as figures, numbered consecutively, not included in the body of the text and all captions should be typed on a separate piece of paper.

Colored illustrations cannot usually be accepted unless the author is prepared to assist with the cost of reproduction.

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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This journal is indexed by **Index Medicus, Excerpta Medica** and **Current Contents — Clinical Practice and Life Science.**

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THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES **VOL. 9, NO. 2 MAY 1982**

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.

See outside back cover.

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Prolopa® Roche®

Rx Summary

Indications
Treatment of Parkinson's syndrome with the exception of drug induced parkinsonism.

Contraindications
Known hypersensitivity to levodopa and/or benserazide.
In patients in whom sympathomimetic amines are contraindicated; in conjunction with monoamine oxidase inhibitors or within two weeks of their withdrawal. Clinical or laboratory evidence of uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; narrow-angle glaucoma (may be used in wide-angle glaucoma provided intraocular pressure remains under control).

Warnings
Discontinue levodopa therapy at least 12 hours before initiating 'Prolopa' therapy. See Dosage section for substitution recommendations.
Increase dosage of 'Prolopa' 100-25 gradually to avoid inducing CNS side effects (abnormal movements). Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Caution in patients with history of psychotic disorders or those receiving reserpine, phenothiazines or tricyclic antidepressants.
Administer with care to patients with history of myocardial infarction or who have atrial, nodal or ventricular arrhythmias.
Safety in patients under 18 years has not been established.
In women who are or may become pregnant benefits should be weighed against possible hazards to mother and fetus. Should not be given to nursing mothers.
Administer with caution to patients with history of melanoma or suspicious undiagnosed skin lesions.

Precautions
Caution in patients with history of convulsive disorders.
Upper gastrointestinal hemorrhage possible in patients with a history of peptic ulcer.
Normal activity should be resumed gradually to avoid risk of injury.
Administer with caution to patients on antihypertensive medication. 'Prolopa' may be discontinued 12 hours prior to anesthesia.
Monitor intraocular pressure in patients with chronic wide-angle glaucoma.

Adverse Reactions
Most common are abnormal involuntary movements, usually dose dependent, which may disappear or become tolerable after dosage reduction.
Most serious after prolonged therapy are periodic oscillations in performance (end of dose akinesia, on-off phenomenon and akinesia paradoxica).
Nausea, vomiting, arrhythmias and orthostatic hypotension occur less frequently than with levodopa alone.
Psychiatric disturbances, including mild elation, depression, anxiety, agitation, aggression, hallucinations and delusions have been encountered.
Consult monograph for complete list of reported adverse effects.

Dosage
Recommended initial dose is one capsule 'Prolopa' 100-25 once or twice daily, increased carefully by one capsule every third or fourth day until an optimum therapeutic effect is obtained without dyskinesias. At upper limits of dosage, increments should be made slowly at 2 to 4 week intervals.
Optimal dosage for most patients is 4 to 8 capsules of 'Prolopa' 100-25 daily (400-800 mg levodopa) divided into 4 to 6 doses. Most patients require no more than 6 capsules 'Prolopa' 100-25 (600 mg levodopa) per day. 'Prolopa' 50-12.5 capsules should be used when frequent dosing is required to minimize adverse effects.
'Prolopa' 200-50 capsules are intended only for maintenance therapy once the optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patients should receive more than 5 to 6 capsules 'Prolopa' 200-50 daily (1000 to 1200 mg levodopa) during the first year of treatment.
For patients previously treated with levodopa, discontinue this medication for 12 hours and initiate treatment with 'Prolopa' 100-25 or 'Prolopa' 50-12.5 so as to provide approximately 15% of the previous levodopa dosage. The initial daily dose, however, should not exceed 6 capsules 'Prolopa' 100-25 divided into 4 to 6 doses.
It is recommended that the capsules be swallowed whole and not be opened or dissolved in liquid.

Supply
Blue, light grey-coloured capsules imprinted ROCHE C and PROLOPA 50-12.5 (black ink) alternating between body and cap, each containing 50 mg levodopa and 12.5 mg benserazide.
Blue, flesh-coloured capsules imprinted ROCHE C and PROLOPA 100-25 (black ink) alternating between body and cap, each containing 100 mg levodopa and 25 mg benserazide.
Blue, caramel-coloured capsules imprinted ROCHE C and PROLOPA 200-50 (black ink) alternating between body and cap, each containing 200 mg levodopa and 50 mg benserazide.
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Product monograph available on request.

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'Prolopa' is listed in provincial formularies.

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Brief Prescribing Information

℞ **Lioresal®** baclofen

Action

The precise mechanisms of action of **Lioresal** (baclofen) are not fully known. It inhibits both monosynaptic and polysynaptic reflexes at the spinal level, probably by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although **Lioresal** is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. Peak plasma concentrations of **Lioresal** are achieved within 2 hours and the plasma half-life is 2-4 hours.

Indications and Clinical Uses

Lioresal (baclofen) is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis.

Lioresal may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

Contraindications

Hypersensitivity to **Lioresal** (baclofen).

Warnings

Abrupt Drug Withdrawal: Following abrupt withdrawal of **Lioresal** (baclofen), visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, insomnia, and worsening of spasticity have occurred. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued. *Impaired Renal Function:* Because **Lioresal** is primarily excreted unchanged through the kidneys, it should be given with caution, and it may be necessary to reduce the dosage. *Stroke:* **Lioresal** has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug. *Pregnancy:* Safe use of **Lioresal** during pregnancy or lactation has not been established. High doses are associated with an increased incidence of abdominal hernias in the fetuses of rats and of ossification defects in those of rats and rabbits. Therefore, the drug should be administered to pregnant patients, or women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Precautions

Safe use of **Lioresal** (baclofen) in children under age 12 has not been established and it is, therefore, not recommended for use in children. Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of **Lioresal** may be additive to those of alcohol and other CNS depressants. **Lioresal** should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function. Extreme caution should be exercised in patients with epilepsy or a history of convulsive disorders. In such patients, the clinical state and electroencephalogram should be monitored at regular intervals during therapy, as deterioration in seizure control and EEG has been reported occasionally in patients taking **Lioresal.** Caution should be used in treating patients with peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and in patients receiving antihypertensive therapy. It is not known whether **Lioresal** is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Adverse Reactions

The most common adverse reactions associated with **Lioresal** (baclofen) are transient drowsiness, dizziness, weakness and fatigue. Others reported: *Neuropsychiatric:* Headache (<10%), insomnia (<10%), and, rarely, 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 (<10%), rare instances of dyspnea, palpitation, chest pain, syncope. *Gastrointestinal:* Nausea, (approx. 10%), constipation (<10%), and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool. *Genitourinary:* Urinary frequency (<10%), and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria. *Other:* Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion. Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

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

Symptoms and Treatment of Overdosage

Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures. The signs and symptoms may be further aggravated by coadministration of a variety of other agents including alcohol, diazepam, and tricyclic antidepressants. *Treatment:* The treatment is symptomatic. In the alert patient, empty the stomach promptly by induced emesis followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. A high urinary output should be maintained since **Lioresal** (baclofen) is excreted mainly by the kidneys. Dialysis is indicated in severe poisoning associated with renal failure.

Dosage and Administration

The determination of optimal dosage of **Lioresal** (baclofen) requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily).

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (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. *Description:* 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.

References:

1. R.F. Jones, J.W. Lance, Medical Journal of Australia, 1976, May:654-657.
2. R.G. Feldman: Symposia Reporter, Vol. 3, No. 2 June 1979.
3. Lioresal Product Monograph.

Product monoraph supplied on request.

PAAB CCPP

Geigy Dorval, Qué. H9S 1B1 G-0018

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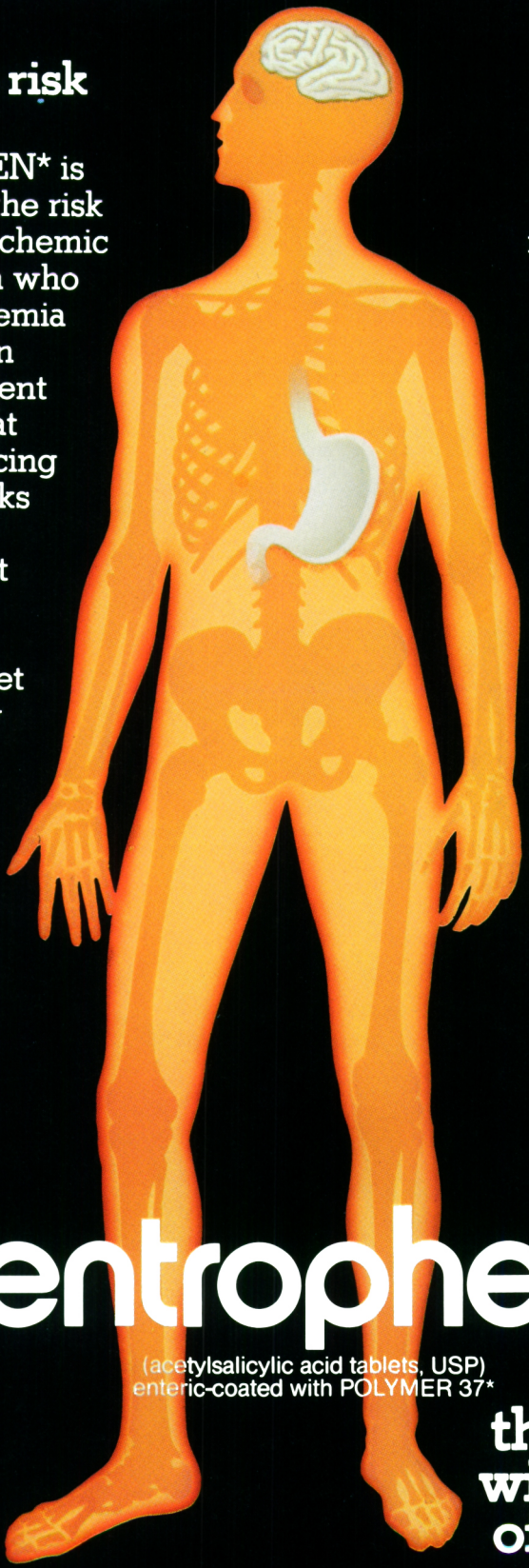
NOW IN STROKE

The Advantages of ENTROPHEN*

To reduce the risk of stroke

Now, ENTROPHEN* is indicated for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. At present there is no evidence that ASA is effective in reducing transient ischemic attacks in women, or is of benefit in the treatment of completed strokes in men or women.

Inhibition of platelet cyclooxygenase activity by a single dose of ENTROPHEN*-10 was comparable to that of plain ASA, although the effect was delayed, reflecting the delayed appearance of ASA in the plasma.[1]



with reduced risk of stomach upset

When you prescribe ASA for long-term use, it is important not to create additional problems for your patients.

While they may benefit from the therapeutic effect of ASA, there is still a potential for gastric irritation and upset, particularly when the regimen calls for continuous daily dosage.

Clinical experience has shown that ENTROPHEN*, coated with POLYMER 37* reduces gastric distress in long-term treatment with high doses of ASA.

entrophen*

(acetylsalicylic acid tablets, USP)
enteric-coated with POLYMER 37*

To reduce the risk of stroke with reduced risk of stomach upset

Frosst
CHARLES E. FROSST & CO.

1. Ali, M. et al.: Plasma acetylsalicylate and salicylate and platelet cyclooxygenase activity following plain and enteric-coated aspirin. Stroke *11(1)*:9-13, Jan/Feb 1980.

*Trademark

https://doi.org/10.1017/S0317167100043699

TABLETS

entrophen*

(acetylsalicylic acid tablets, USP)

Enteric-coated with POLYMER 37*

Anti-inflammatory—Analgesic Agent

Platelet Aggregation Inhibitor

DESCRIPTION

ENTROPHEN* is an enteric-coated tablet containing acetylsalicylic acid coated with POLYMER 37*, a partially esterified polyvinyl alcohol.

ACTION

Acetylsalicylic acid (ASA) has analgesic, antipyretic and anti-inflammatory properties.

In rheumatic diseases, although the analgesic and antipyretic effects are useful, the major purpose for which ASA is used is to reduce the intensity of the inflammatory process. Inhibition of prostaglandin synthesis may be involved in the anti-inflammatory action of ASA.

ASA also alters platelet aggregation and release reaction by inhibiting prostaglandin synthesis Thromboxane A_2 is an essential step in platelet aggregation. ASA prevents Thromboxane A_2 formation by acetylation of platelet cyclooxygenase. This inhibition of prostaglandin synthesis is irreversible and affects platelet function for the life of the platelet.

The POLYMER 37* coating substantially resists disintegration in aqueous fluids having a pH lower than 3.5 for a period of at least 2 hours and is capable of disintegrating in aqueous fluids having a pH of at least 5.5 in from 10 to 30 minutes. Thus, POLYMER 37* coating effectively inhibits the release of ASA in the stomach, whilst allowing the tablet to dissolve in the upper portion of the small intestine for absorption from the duodenal area.

Clinical experience has shown that POLYMER 37* coated acetylsalicylic acid diminishes or eliminates gastric distress during long-term treatment with high doses of ASA.

INDICATIONS

ENTROPHEN* is indicated whenever gastric intolerance to ASA is of concern.

ENTROPHEN* is indicated for the relief of signs and symptoms of the following:

Osteoarthritis
Rheumatoid arthritis
Spondylitis
Bursitis
and other forms of rheumatism
Musculoskeletal disorders

Rheumatic fever, however, penicillin and other appropriate therapy should be administered concomitantly.

ASA is generally considered to be the primary therapy for most forms of arthritis.

ENTROPHEN* is also indicated for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. At present there is no evidence that ASA is effective in reducing transient ischemic attacks in women, or is of benefit in the treatment of completed strokes in men or women.

CONTRAINDICATIONS

Sensitivity to the ingredients
Active peptic ulcer
Patients who had a bronchospastic reaction to ASA or non-steroidal anti-inflammatory drugs.

WARNINGS

ASA is one of the most frequent causes of accidental poisoning in toddlers and infants. ENTROPHEN* should, therefore, be kept well out of the reach of all children.

PRECAUTIONS

Salicylates should be administered with caution to patients with asthma and other allergic conditions, with a history of gastrointestinal ulcerations, with bleeding tendencies, with significant anemia or with hypoprothrombinemia.

Salicylates can produce changes in thyroid function tests.

Acute hepatitis has been reported rarely in patients with systemic lupus erythematosus and juvenile rheumatoid arthritis with plasma salicylate concentrations above 25 mg/100 mL. Patients have recovered upon cessation of therapy.

Use in Pregnancy

ASA does not appear to have any teratogenic effects. ASA has been found to delay parturition in rats. This effect has also been described with non-steroidal anti-inflammatory agents which inhibit prostaglandin synthesis.

High doses (3 g daily) of ASA during pregnancy may lengthen the gestation and parturition time.

Because of possible adverse effects on the neonate and the potential for increased maternal blood loss, ASA should be avoided during the last three months of pregnancy.

Drug Interactions

Caution is necessary when ENTROPHEN* and anticoagulants are prescribed concurrently, as ASA may potentiate the action of anticoagulants.

Salicylates may potentiate sulfonylurea hypoglycemic agents. Large doses of salicylates may have a hypoglycemic action, and thus, affect the insulin requirements of diabetics.

Although salicylates in large doses are uricosuric agents, smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of probenecid, sulfinpyrazone and phenylbutazone.

Sodium excretion produced by spironolactone may be decreased in the presence of salicylates.

Salicylates also retard the renal elimination of methotrexate.

ADVERSE REACTIONS

Gastrointestinal reactions: nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration. Ear reactions: tinnitus, vertigo, hearing loss. Hematologic reactions: leukopenia, thrombocytopenia, purpura. Dermatologic and Hypersensitivity reactions: urticaria, angioedema, pruritus, various skin eruptions, asthma and anaphylaxis. Miscellaneous reactions: acute reversible hepatotoxicity, mental confusion, drowsiness, sweating and thirst.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In mild overdosage these may include rapid and deep breathing, nausea, vomiting (leading to alkalosis), hyperpnea, vertigo, tinnitus, flushing, sweating, thirst and tachycardia. (High blood levels of ASA lead to acidosis.) Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma, and respiratory failure.

Treatment

Treatment is essentially symptomatic and supportive. Administer water, universal antidote and remove by gastric lavage or emesis. Force fluids (e.g., salty broth) to replace sodium loss. If the patient is unable to retain fluids orally, the alkalosis can be treated by hypertonic saline intravenously. If salicylism acidosis is present, sodium bicarbonate intravenously is preferred because it increases the renal excretion of salicylates. Vitamin K is indicated if there is evidence of hemorrhage. Hemodialysis has been used with success.

Respiratory depression may require artificial ventilation with oxygen. Convulsions may best be treated by the administration of succinylcholine and artificial ventilation with oxygen. Central nervous system depressant agents should not be used.

Hyperthermia and dehydration are immediate threats to life and initial therapy must be directed to their correction and to the maintenance of adequate renal function. External cooling with cool water or alcohol should be provided quickly to any child who has a rectal temperature over 104°F.

DOSAGE AND ADMINISTRATION

Analgesic; antipyretic

Up to 2.925 g daily as necessary.

Anti-inflammatory

Because the suppression of inflammation increases with the dose of salicylate even beyond the point of toxicity, the therapeutic objective is to employ as large a dose as possible short of toxicity. Most patients will tolerate blood salicylate levels in the range of 20 to 25 mg per cent. The most common reason for failing to obtain a therapeutic response to ASA is the administration of inadequate doses.

The generally accepted way to achieve effective 'anti-inflammatory' salicylate blood levels of 20 to 25 mg per cent is to titrate the dosage by starting with 2.6 to 3.9 g daily, according to the size, age and sex of the patient. If necessary, the dosage is then gradually adjusted by daily increments of 0.65 g until symptoms of salicylism e.g., auditory symptoms, occur. Then, the dosage is decreased by 0.65 g daily until these symptoms disappear and maintained at that level as long as necessary.

In adults the median dose at which tinnitus develops is 4.5 g per day, but the range extends from 2.6 to 6.0 g per day.

Intermittent administration is ineffective. Patients should be advised not to vary the dose from day to day depending on the level of pain because that often fluctuates independently of the intensity of the inflammation. A continuous regimen of 0.65 g four times daily is considered to be minimum therapy for adults. ENTROPHEN* should be administered four times daily. For nighttime and early morning benefits, the last dose should be given at bedtime.

Once maintenance dose is established, ENTROPHEN*-15 may be useful to encourage patient compliance.

Optimally, salicylate therapy should be monitored by periodic blood salicylate level determinations. If this is not practical, the appearance of auditory symptoms in the form of tinnitus or deafness are acceptable as an indication of the maximum tolerated salicylate dose.

There is an inverse relation between blood salicylate levels at which auditory symptoms appear and the age of the patient. In the young adult, this is usually in the range of 20 to 30 mg per cent. In children, however, the level may be much higher, or the effect apparently absent. Because salicylate toxicity may appear without such warning in children, the usual practice is to give ASA in a daily dose of 50 to 100 mg per kilogram of body weight and to follow blood levels aiming for a concentration of about 30 mg per cent.

Rheumatic Fever

A total daily dosage of 100 mg per kilogram of body weight administered in divided doses to allay the pain, swelling and fever.

Cerebral ischemic attacks (men)

The recommended dosage is 1,300 mg per day (650 mg twice a day or 325 mg four times a day).

AVAILABILITY

No. 472—ENTROPHEN*-15 tablets containing 975 mg of acetylsalicylic acid USP, coated with POLYMER 37*. Oval, pale yellow, film-coated tablets with the FROSST name engraved on one face and 472 on the other and supplied in bottles of 100 and 500.

No. 470—ENTROPHEN*-10 tablets containing 650 mg of acetylsalicylic acid USP, coated with POLYMER 37*. Oval, orange, film-coated tablets, with the FROSST name engraved on one face and 470 on the other and supplied in bottles of 100, 500 and 1,000.

No. 438—ENTROPHEN*-5 tablets containing 325 mg of acetylsalicylic acid USP, coated with POLYMER 37*. Round, brown, film-coated tablets, with the FROSST name engraved on one face and 438 on the other and supplied in bottles of 100, 500 and 1,000.

FULL PRODUCT MONOGRAPH AVAILABLE ON REQUEST.

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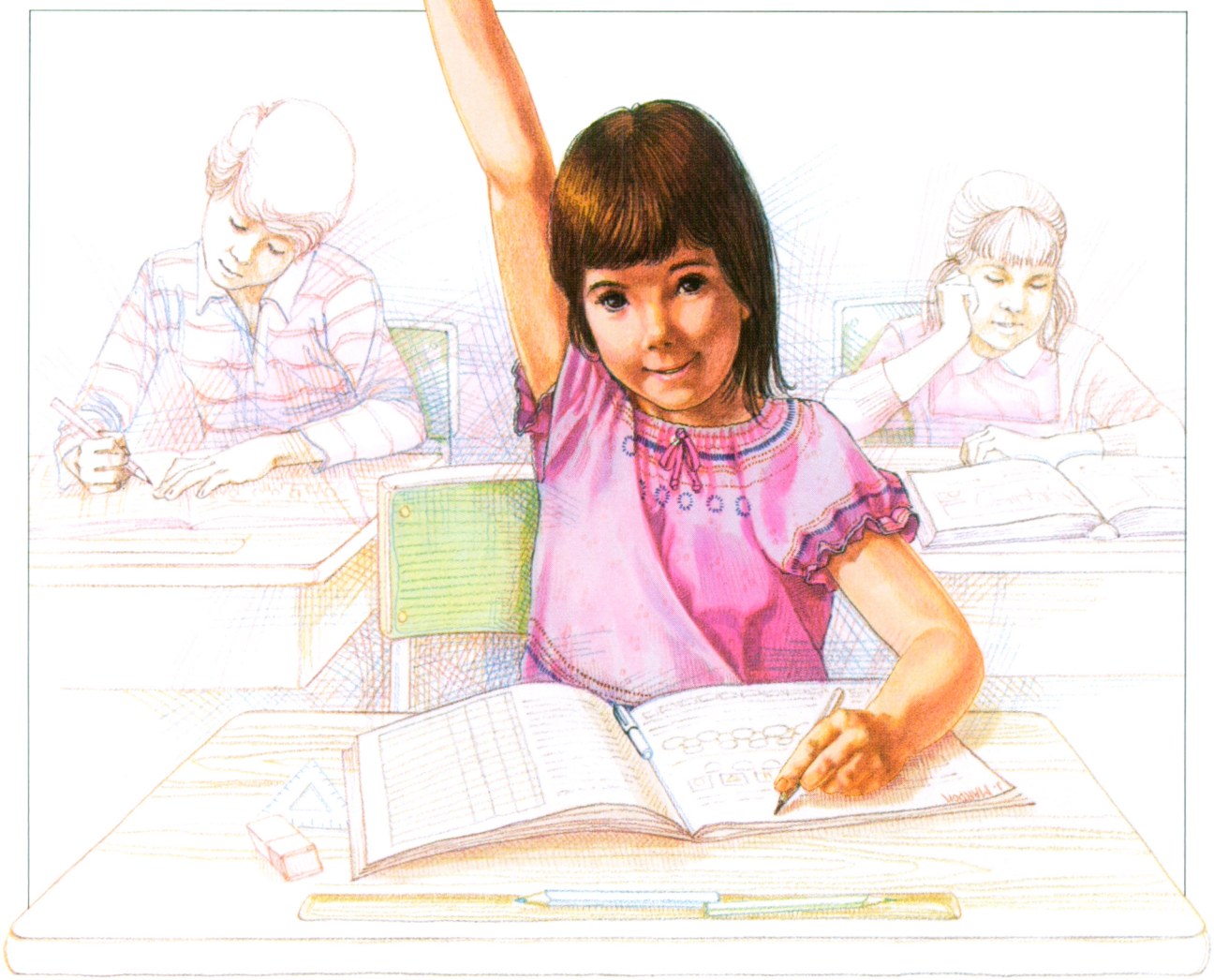
you wouldn't guess Jane's an epileptic



Epileptic therapy doesn't have to interfere with her life. Depakene can effectively control seizures, with little risk of disturbed behaviour or poor performance.

Depakene provides broad-spectrum seizure control Depakene is considered a drug of first choice for simple and complex absence seizures[1,2] and has been successfully used in tonic-clonic or myoclonic seizures with absence components.[3,4]

No impairment of learning Depakene has made patients more alert, more lively and better able to perform daily tasks.[5]

Positive effect on behaviour Depakene, unlike phenobarbital, rarely affects behaviour, and may actually improve it.[5]

Low incidence of disturbing side effects Depakene does not cause hirsutism, gum hyperplasia or acne, nor has it been associated with aplastic anemia or agranulocytopenia.

Minimizes problems of polypharmacy Depakene is often effective as single therapy. When other anticonvulsants are necessary, their dosage may be reduced.

New dosage convenience A 500-mg enteric-coated capsule is now available.

valproic acid

Depakene*

brings many epileptic patients closer to normal

PHARMACEUTICAL PRODUCTS DIVISION
ABBOTT LABORATORIES, LIMITED
MONTREAL, CANADA H4P 1A5

*TM

MEMBER PMAC PAAB

Prescribing information on page . . .

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Depakene

valproic acid

Brief prescribing information

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) should not be administered to patients with hepatic disease or significant dysfunction; it is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving Depakene. These incidences usually have occurred during the first six months of treatment with Depakene. 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 nonspecific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious causes while taking sodium valproate.
Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering Depakene 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, valproic acid 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 dysfunctions, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects particularly elevated liver enzymes may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

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 three-fold. 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 to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.
Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

NURSING MOTHERS: Depakene is secreted 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 valproic acid.

FERTILITY: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of Depakene (valproic acid) on the development of the testes and on sperm production and fertility in humans is unknown.
LONG TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS: HEPATIC DYSFUNCTION: SEE CONTRAINDICATIONS AND WARNINGS

GENERAL: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving Depakene (valproic acid) be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of Depakene (valproic acid) 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 valproic acid should be discontinued.
Because Depakene (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). There have been reports of breakthrough seizures occurring with the combination of Depakene and phenytoin.
Depakene (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.
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. 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.

ENDOCRINE: There have been reports of irregular menses and secondary amenorrhea in patients receiving Depakene.

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

MUSCULOSKELETAL: Weakness has been reported.

HEMATOPOIETIC: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (see DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

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

METABOLIC: Hyperammonemia. (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing nonketotic hyperglycinemia.

PANCREATIC: Isolated reports of pancreatitis in association with valproic acid therapy have been received.

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.
Naloxone has been reported to reverse the CNS depressant effects of Depakene overdose. Because naloxone could theoretically also reverse the anticonvulsant effects of Depakene it should be used with caution.
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 maximal recommended dose is 60 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen. A 500-mg enteric coated capsule may be substituted for two 250-mg capsules.
The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased 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 Dose (mg)	Number of Capsules or Teaspoonfuls 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. Such patients may benefit from administration of the enteric-coated capsule. 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 capsules (Number 5681; DIN 443840); pale yellow, oval soft gelatin enteric-coated capsules of 500 mg in bottles of 100 capsules (Number D795; DIN 507989) 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 (Number 5682; DIN 443832).

Depakene is now available in a 500-mg enteric-coated capsule.

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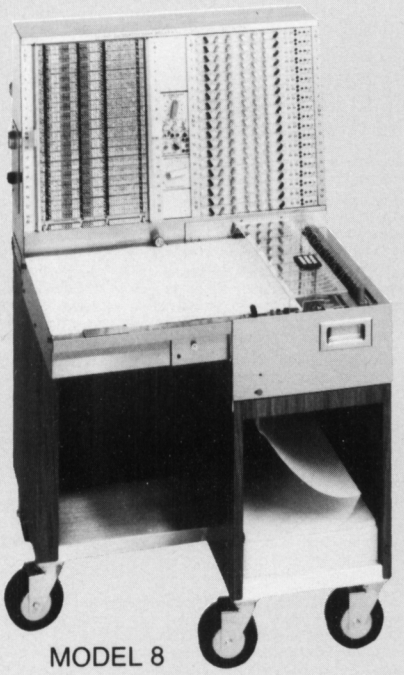
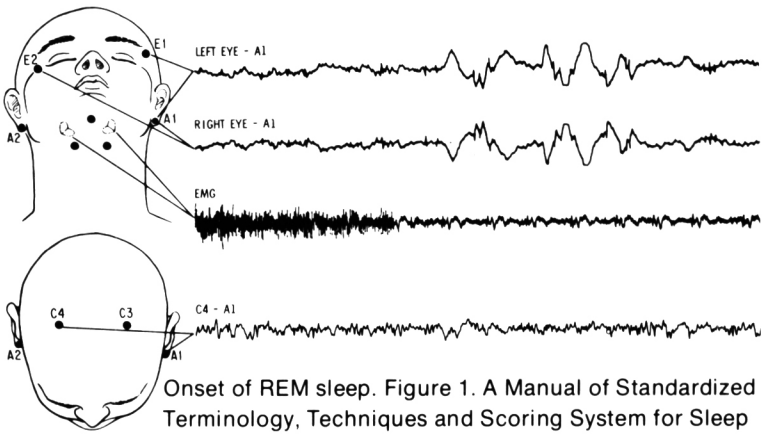
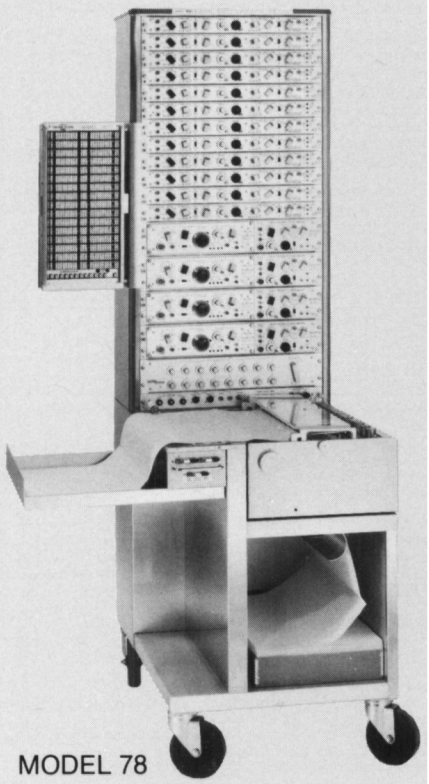


MODEL 8

POLYSOMNOGRAPHIC RECORDING FOR CLINIC OR RESEARCH



Onset of REM sleep. Figure 1. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. UCLA-BIS-DHEW.



MODEL 78

For multiple parameter recording of sleep-wake disorders in the clinical or the research setting, Grass Polygraphs and EEGs have the reliability and flexibility required.

For research applications, the Model 78 Polygraph with a wide selection of interchangeable signal conditioning preamplifiers allows recording several channels of EEG, EOG, EMG, ENG, temperature, respiration, EKG, blood gases, etc., with convenience and ease. A wide range of transducers, recording accessories, plus multiple chart speeds, *including the widely used 10 mm/sec,* provide a complete sleep-wake recording system.

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