Epilepsy International Congress — 1981

XIV Congress of International League Against Epilepsy
XIII Symposium of International Bureau for Epilepsy

Organized by:

EPILEPSY INTERNATIONAL

International League Against Epilepsy (ILAE)
International Bureau for Epilepsy (IBE)

JAPAN EPILEPSY SOCIETY
JAPAN EPILEPSY ASSOCIATION

1. INVITATION

It is my great pleasure to extend a cordial invitation to all members of affiliated organizations of Epilepsy International as well as individuals interested in any aspect of epilepsy to attend the Epilepsy International Congress-1981.

This is the first world epilepsy congress to be held in Asia. The Congress is to meet in conjunction with the 10th International Congress of Electroencephalography and Clinical Neurophysiology (ICECN) and the 12th World Congress of Neurology (WCN), so that this Congress will serve as a bridge between the two congresses. We hope to organize a truly world-wide congress with participants from many disciplines and interests.

We sincerely hope that the Congress will be a milestone in helping people with epilepsy and that this old but new ailment will eventually be eradicated from throughout the world.

Haruo Akimoto
Congress President

2. PLACE AND DATE

The Congress will be held from Thursday, September 17 to Monday, September 21, 1981 at the Kyoto International Conference Hall located in the northern outskirts of Kyoto City.

This Congress will therefore be a link between the 10th ICECN (Sept. 13 - 18) and the 12th WCN (Sept. 20 - 26), both to be also held at the Kyoto International Conference Hall.

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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 douleureux). 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.

PAAB
CCPP

Geigy
Dorval, Qué. H9S 1B1

G-9091

Rivotril®

Rx Summary

Indications
Alone or adjunctively in the management of myoclonic, akinetic and petit mal variant seizures. In petit mal (absence spells) when response to succinimides unsatisfactory.
Contraindications
Hypersensitivity to benzodiazepines. Clinical or biochemical evidence of significant liver disease. Narrow angle glaucoma.
Warnings
Use in pregnancy: in women who are or who may become pregnant when potential benefits warrant possible risks to mother and fetus. Mothers receiving 'Rivotril' should not breastfeed infants. Consider the risk/benefit of long-term use, *particularly in children.*
Precautions
Use of multiple anticonvulsants may increase CNS depression and dosage of each may need adjustment downward. Avoid abrupt withdrawal and consider substitution with another anticonvulsant during withdrawal.
May cause paradoxical increase in seizure activity or new seizure types. Concomitant use with valproic acid may produce absence status.
Caution patients against engaging in hazardous activities requiring complete mental alertness or physical coordination. Warn against concomitant use of alcohol or other CNS depressant drugs.
Monitor patients who may be prone to increasing the dosage on their own accord.
Administer with caution to patients with impaired renal function. Periodic liver function tests and blood counts may be advisable during long-term therapy.
Institute therapy with caution in patients with chronic respiratory disease because of possible hypersecretion in upper respiratory tract.
Adverse Reactions
Drowsiness has occurred in 50% and ataxia in 30% of patients but these effects have diminished with time. Behavioural problems have been noted in approximately 25% and increased salivation in 7% of patients.
Consult monograph for complete list of reported adverse reactions.
Dosage
Depends upon age and must be determined according to clinical response and tolerance.
Daily requirements should be given in 2 or 3 divided doses and if not equal, the larger dose should be given before retiring.
Children up to 10 years (30 kg): Initial dose should be 0.01 to 0.03 mg/kg/day and should not exceed 0.05 mg/kg/day. Increase dose by 0.25 to 0.5 mg every third day to maintenance dose of 0.1 to 0.2 mg/kg/day providing optimum response.
Adults: Initial dose should not exceed 1.5 mg/day. Increase dose by 0.5 to 1.0 mg every third day to maintenance dose of 8 to 10 mg/day with optimum response. Dosage in excess of 20 mg/day should be administered with caution.
Bear in mind possible increased depressant effects whenever 'Rivotril' is added to an existing anticonvulsant regimen.
Supply
Orange, cylindrical, biplane tablets with RIVOTRIL 0.5 engraved on one face, and single scored on the other with ROCHE above and C below the score, each containing 0.5 mg clonazepam.
White, cylindrical, biplane tablets with RIVOTRIL 2 engraved on one face, and single scored on the other with ROCHE above and C below the score, each containing 2 mg clonazepam.
Bottles of 100.
References
1. Shakir, R.A. et al: *Arch. Neurol.* **36**:302, May 1979.
2. Bruni, J.: *CMAJ* **120**:819, April 7, 1979.
3. Browne, T.R.: *New Eng. J. Med.* (Ed.), **299**:812-816, Oct. 1978.

Product Monograph available on request.
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Original Research in Medicine and Chemistry

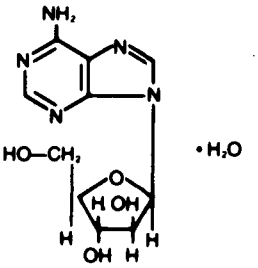
Vira-A

(Sterile Vidarabine for Infusion)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Antiviral Agent

STRUCTURAL FORMULA AND CHEMISTRY



Molecular Formula: $C_{10}H_{13}N_5O_4.H_2O$

Molecular Weight: 285.2

Chemical Name: 9-β-D-arabinofuranosyl-adenine monohydrate.

Description: Vira-A (Vidarabine) is a white, crystalline solid. The solubility is 0.45 mg/ml at 25°C; and the melting point ranges from 260° to 270°C.

Action. Vira-A, an antiviral drug, is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against *Herpesvirus* Simplex (Herpes Simplex virus) types 1 and 2.

The antiviral mechanism of action has not yet been established. The drug is converted into nucleotides which appear to be involved with the inhibition of viral replication. In KB cells infected with Herpes Simplex virus type 1, Vira-A inhibits viral DNA synthesis.

Excretion of Vira-A is principally via the kidneys. Vira-A is rapidly deaminated to Ara-Hx (arabinosylhypoxanthine), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is significantly less than Vira-A. Forty-one to 53% of the daily dose is cumulatively recovered in the urine as Ara-Hx with 1 to 3% appearing as the parent compound. Steady state urinary excretion of Vira-A and Ara-Hx is attained by day 3 following the first infusion. The urinary excretion rate of Vira-A is generally constant over the 12 hours during infusion and the 12 hours post-infusion. There is no evidence of fecal excretion of drug or metabolite.

Indications and Clinical Use. Vira-A is indicated in the treatment of Herpes Simplex virus encephalitis. Controlled studies indicate that Vira-A therapy reduced the mortality rate due to Herpes Simplex virus encephalitis from 70 to 28%.

Vira-A treatment has no beneficial effect on the neurological sequelae present at the time of initiation of therapy. Therefore, early diagnosis and treatment are essential.

Herpes Simplex virus encephalitis should be suspected in patients with a history of an acute febrile encephalopathy associated with disordered mentation, altered level of consciousness and focal cerebral signs.

Studies which may support the suspected diagnosis include examination of cerebrospinal fluid and localization of an "intra-cerebral lesion" by brain scan, electroencephalography or computerized axial tomography (CAT).

Brain biopsy is required in order to confirm the etiological diagnosis by means of viral isolation in cell cultures.

Detection of Herpes Simplex virus in the biopsied brain tissue can also be reliably done by specific fluorescent antibody techniques. Detection of Herpes virus-like particles by electron microscopy or detection of intranuclear inclusions by histopathologic techniques only provides a presumptive diagnosis.

There are no reports available to indicate that Vira-A for infusion is effective in the management of encephalitis due to varicella-zoster or vaccinia viruses. Vira-A is not effective against infections caused by adenovirus or RNA viruses. It is also not effective against bacterial or fungal infections. There are no data to support efficacy of Vira-A against cytomegalovirus, vaccinia virus, or smallpox virus.

Contraindications. Vira-A is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. Vira-A should not be administered by the intramuscular or subcutaneous route because of its low solubility and poor absorption.

Precautions. Treatment should be discontinued in the patients with a brain biopsy negative for Herpes Simplex virus in cell culture, unless an obvious diagnosis of Herpes Simplex encephalitis is strongly suspected on the basis of patient history and clinical evaluation.

Special care should be exercised when administering Vira-A to patients susceptible to fluid overloading or cerebral edema. Examples are patients with CNS infections and impaired renal function.

Patients with impaired renal function, such as post-operative renal transplant recipients, may have a slower rate of renal excretion of Ara-Hx. Therefore, the dose of Vira-A may need to be adjusted according to the severity of impairment. These patients should be very carefully monitored.

Patients with impaired liver function should also be monitored for possible adverse effects.

Appropriate hematologic tests are recommended during Vira-A administration since hemoglobin, hematocrit, white blood cells, and platelets may be depressed during therapy.

In addition to hematologic values, close monitoring of liver function, renal function, and neurological status is strongly encouraged while using Vira-A.

A case of post-infectious encephalomyelitis resulting in a lasting mental impairment of the patient has been reported after an initially successful treatment of Herpes Simplex encephalitis with Vira-A. A second course of treatment with the same drug did not alleviate the symptoms. It is important to monitor this complication in patients who survive the acute encephalitic phase of herpes simplex virus infection.

Some degree of immunocompetence must be present in order for Vira-A to achieve clinical response.

Usage In Pregnancy. Vira-A given parenterally is teratogenic in rats and rabbits. Doses of 5 mg/kg or higher given intramuscularly to pregnant rabbits during organogenesis induced fetal abnormalities. Doses of 3 mg/kg or less did not induce teratogenic changes in pregnant rabbits. Vira-A doses ranging from 30 to 200 mg/kg were given intramuscularly to pregnant rats during organogenesis; signs of maternal toxicity were induced at doses of 100 mg/kg or higher and frank fetal anomalies, with an incidence of >90%, were found at dose levels of 150 mg/kg and higher. Lower doses (30-100 mg/kg) had inconsistent, though positive, effects.

A safe dose for the human embryo or fetus has not been established. Consequently, the use of Vira-A in pregnant patients should be limited to life-threatening illnesses where the possible benefits outweigh the potential risks involved.

It is not known whether Vira-A is excreted in human milk. As a general rule nursing should not be undertaken while a patient is under treatment since many drugs are excreted in human milk. However, Vira-A is rapidly deaminated in the gastro-intestinal tract.

Adverse Reactions. The principal adverse reactions involve the gastro-intestinal tract and are anorexia, nausea, vomiting, and diarrhea. These reactions are usually mild to moderate, and seldom require termination of Vira-A therapy. Occasional cases with severe discomfort requiring cessation of therapy have been reported.

Neurological complications have been reported at therapeutic doses. These are tremor, dizziness, hallucinations, disorientation, major motor seizures, confusion, psychosis, and ataxia.

Hematologic clinical laboratory changes noted in controlled studies were a decrease in hemoglobin or hematocrit, total white blood cells, granulocytes and platelets. SGOT elevations were also observed. Other changes occasionally observed were decreases in reticulocyte count and elevated total bilirubin.

Other symptoms which have been reported are sharp pain of parotid or masseter muscles, weight loss, malaise, pruritus, rash, hematemesis, and pain at the injection site.

Symptoms and Treatment Of Overdosage. Acute massive overdose of the intravenous form has been reported without any serious evidence of adverse effect. Acute water overloading would pose a greater threat to the patient than Vira-A, due to its low solubility. Doses of Vira-A over 20 mg/kg/day can produce bone marrow depression with concomitant thrombocytopenia and leukopenia. If a massive overdose of the intravenous form occurs, hematologic, neurologic, liver, and renal functions should be carefully monitored. Treatment should be chiefly symptomatic.

Acute massive oral ingestion is not expected to be toxic because drug absorption from the gastrointestinal tract is minimal. The oral LD_{50} for Vira-A is greater than 5,020 mg/kg in mice and rats.

Dosage and Administration. CAUTION—THE CONTENTS OF THE VIAL MUST BE DILUTED IN AN APPROPRIATE INTRAVENOUS SOLUTION PRIOR TO ADMINISTRATION. RAPID OR BOLUS INJECTION MUST BE AVOIDED.

Dosage. Herpes Simplex virus encephalitis 15 mg/kg/day for 10 days.

Method of Preparation. Each vial contains 200 mg of Vira-A per ml of suspension. The solubility of Vira-A in intravenous infusion fluids is limited. Each one mg of Vira-A requires 2.22 ml of intravenous infusion fluid for complete solubilization. Therefore, each one litre of intravenous infusion fluid will solubilize a maximum of 450 mg of Vira-A.

The following intravenous infusion fluids are compatible with Vira-A and may be used as diluents:

5% Dextrose injection USP

5% Dextrose plus 0.9%, 0.33% or 0.45% sodium chloride injection USP *or* Lactated Ringer's injection USP.

Biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not suitable as diluents.

Shake the Vira-A well to obtain a homogeneous suspension before measuring and transferring.

Prepare the Vira-A solution for intravenous administration by aseptically transferring the proper dose of Vira-A into an appropriate intravenous infusion fluid. The intravenous infusion fluid used to prepare the Vira-A solution may be prewarmed to 36° to 40°C (95° to 100°F) to facilitate solution of the drug following its transference. Depending on the dose to be given, more than one litre of intravenous infusion fluid may be required. Thoroughly agitate the prepared admixture until *completely* clear. Complete solubilization of the drug, as indicated by a completely clear solution, is ascertained by careful visual inspection. Final filtration with an in-line membrane filter (0.45 μ pore size or smaller) is necessary.

Dilution should be made just prior to administration and the solution should be used within 48 hours. Any unused portion should be discarded.

Administration. Using aseptic technique, slowly infuse the total daily dose by intravenous infusion (prepared as discussed above) at a constant rate over a 12- to 24-hour period.

Availability. Vira-A (Vidarabine for Infusion), a sterile suspension containing 200 mg/ml is supplied in 5 ml Steri-Vials; packages of 10.

Animal Toxicology

Acute Toxicity. The intraperitoneal LD_{50} for Vira-A ranged from 3,890 to 4,500 mg/kg in mice, and from 2,239 to 2,512 mg/kg in rats, suggesting a low order of toxicity to a single parenteral dose. Hepatic megalocytosis was observed in rats after single, intraperitoneal injections at doses near and exceeding the LD_{50} value. The hepatic megalocytosis appeared to regress over several months. Acute intravenous LD_{50} values could not be obtained because of the limited solubility of Vira-A.

Subacute Toxicity. Rats, dogs, and monkeys have been given daily intramuscular injections of Vira-A as a 20% suspension for 28 days. These animal species showed dose related decreases in hemoglobin, hematocrit, and lymphocytes. Bone marrow depression was also observed in monkeys. Except for localized, injection-site injury and weight gain inhibition or loss, rats tolerated daily doses up to 150 mg/kg, and dogs tolerated daily doses up to 50 mg/kg. Megalocytosis was not seen in the rats dosed by the intramuscular route for 28 days.

In rats, all drug-treated males and the high and mid-dose females had moderate to marked increase in spleen weight at the end of the treatment period.

Rhesus monkeys were particularly sensitive to Vira-A. Daily intramuscular doses of 15 mg/kg were tolerable, but doses of 25 mg/kg or higher induced progressively severe clinical signs of CNS toxicity. Three monkeys given slow intravenous infusions of Vira-A in solution at a dose of 15 mg/kg daily for 28 days had no significant adverse reactions.

Tumorigenicity. Chronic parenteral (IM) studies of vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant increase in liver tumor incidence among the vidarabine-treated females. In the same study, some vidarabine-treated male mice developed kidney neoplasia. No renal tumors were found in the vehicle-treated control mice or the vidarabine-treated female mice.

In the rat study, intestinal, testicular, and thyroid neoplasia occurred with greater frequency among the vidarabine-treated animals than in the vehicle-treated controls. The increases in thyroid adenoma incidence in the high-dose (50 mg/kg) males and the low-dose (30 mg/kg) females were statistically significant.

Hepatic megalocytosis, associated with vidarabine treatment, has been found in short- and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.

Mutagenicity. Results of *in vitro* experiments indicate that vidarabine can be incorporated into mammalian DNA and can induce mutation in mammalian cells (mouse L5178Y cell line). Thus far, *in vivo* studies have not been as conclusive, but there is some evidence (dominant lethal assay in mice) that vidarabine may be capable of producing mutagenic effects in male germ cells.

It has also been reported that vidarabine causes chromosome breaks and gaps when added to human leukocytes *in vitro*. While the significance of these effects in terms of mutagenicity is not fully understood, there is a well-known correlation between the ability of various agents to produce such effects and their ability to produce heritable genetic damage.

PARKE-DAVIS

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

Sinemet*

ANTIPARKINSON AGENT

Common adverse reactions that can occur with SINEMET* are abnormal involuntary movements and, less frequently, mental changes. These usually can be diminished by dosage reduction.

INDICATIONS

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

CONTRAINDICATIONS

When a sympathomimetic amine is contraindicated; with monoamine oxidase inhibitors, which should be discontinued two weeks prior to starting SINEMET*; in uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary or renal disease; in narrow-angle glaucoma; in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

When given to patients receiving levodopa alone, discontinue levodopa at least 12 hours before initiating SINEMET* at a dosage that provides approximately 20% of previous levodopa.

Not recommended in drug-induced extrapyramidal reactions; contraindicated in management of intention tremor and Huntington's chorea.

Levodopa related central effects such as involuntary movements may occur at lower dosages and sooner, and the 'on and off' phenomenon may appear earlier with combination therapy.

Monitor carefully all patients for the development of mental changes, depression with suicidal tendencies, or other serious antisocial behaviour.

Cardiac function should be monitored continuously during period of initial dosage adjustment in patients with arrhythmias.

Upper gastrointestinal hemorrhage is possible in patients with history of peptic ulcer.

Safety of SINEMET* in patients under 18 years of age not established.

Pregnancy and lactation: In women of childbearing potential, weigh benefits against risks. Should not be given to nursing mothers. Effects on human pregnancy and lactation unknown.

PRECAUTIONS

General: Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function recommended in extended therapy. Treat patients with history of convulsions cautiously. *Physical Activity:* Advise patients improved on SINEMET* to increase physical activities gradually, with caution consistent with other medical considerations. *In Glaucoma:* May be given cautiously to patients with wide angle glaucoma, provided intraocular pressure is well controlled and can be carefully monitored during therapy. *With Antihypertensive Therapy:* As symptomatic postural hypotension has been reported occasionally, give cautiously to patients on antihypertensive drugs, checking carefully for changes in pulse rate and blood pressure. Dosage adjustment of antihypertensive drug may be required. *With Psychoactive Drugs:* If concomitant administration is necessary, administer psychoactive drugs with great caution and observe patients for unusual adverse reactions. *With Anesthetics:* Discontinue SINEMET* the night before general anesthesia and reinstitute as soon as patient can take medication orally.

ADVERSE REACTIONS

Most Common: *Abnormal Involuntary Movements*—usually diminished by dosage reduction—choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be early signs of excessive dosage.

Other Serious Reactions: Oscillations in performance: diurnal variations, independent oscillations in akinesia with stereotyped dyskinesias, sudden akinetic crises related to dyskinesias, akinesia paradoxica (hypotonic freezing) and 'on and off' phenomenon. Psychiatric: paranoid ideation, psychotic episodes, depression with or without development of suicidal tendencies and dementia. Levodopa may produce hypomania when given regularly to bipolar depressed patients. Rarely convulsions (causal relationship not established). Cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, anorexia, nausea, vomiting and dizziness.

Other adverse reactions that may occur: *Psychiatric:* Increased libido with serious antisocial behaviour, euphoria, lethargy, sedation, stimulation, fatigue and malaise, confusion, insomnia, nightmares, hallucinations and delusions, agitation and anxiety. *Neurologic:* ataxia, faintness, impairment of gait, headache, increased hand tremor, akinetic episodes, "akinesia paradoxica", increase in the frequency and duration of the oscillations in performance, torticollis, trismus, tightness of the mouth, lips or tongue, oculogyric crisis, weakness, numbness, bruxism, priapism. *Gastrointestinal:* constipation, diarrhea, epigastric and abdominal distress and pain, flatulence; eructation, hiccups, sialorrhea; difficulty in swallowing, bitter taste, dry mouth; duodenal ulcer; gastrointestinal bleeding; burning sensation of the tongue. *Cardiovascular:* arrhythmias, hypotension, non-specific ECG changes, flushing, phlebitis. *Hematologic:* hemolytic anemia, leukopenia, agranulocytosis. *Dermatologic:* sweating, edema, hair loss, pallor, rash, bad odor, dark sweat. *Musculoskeletal:* low back pain, muscle spasm and twitching, musculoskeletal pain. *Respiratory:* feeling of pressure in the chest, cough, hoarseness, bizarre breathing pattern, postnasal drip. *Urogenital:* urinary frequency, retention, incontinence, hematuria, dark urine, nocturia, and one report of interstitial nephritis. *Special Senses:* blurred vision, diplopia, dilated pupils; activation of latent Horner's syndrome. *Miscellaneous:* hot flashes, weight gain or loss. Abnormalities in laboratory tests reported with levodopa alone, which may occur with SINEMET*: Elevations of blood urea nitrogen, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase or protein bound iodine. Occasional reduction in WBC, hemoglobin and hematocrit. Elevations of uric acid with colorimetric method. Positive Coombs tests reported both with SINEMET* and with levodopa alone, but hemolytic anemia extremely rare.

DOSAGE SUMMARY

In order to reduce the incidence of adverse reactions and achieve maximal benefit, therapy with SINEMET* must be individualized and drug administration continuously matched to the needs and tolerance of the patient. Combined therapy with SINEMET* has a narrower therapeutic range than with levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and recommended dosage ranges not be exceeded. Appearance of involuntary movements should be regarded as a sign of levodopa toxicity and an indication of overdosage, requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesis.

Therapy in Patients not receiving Levodopa: Initially ½ tablet once or twice a day, increase by ½ tablet every three days if desirable. An optimum dose of 3 to 5 tablets a day divided into 4 to 6 doses.

Therapy in Patients receiving Levodopa: *Discontinue levodopa for at least 12 hours,* then give approximately 20% of the previous levodopa dose in 4 to 6 divided doses.

FOR COMPLETE PRESCRIBING INFORMATION, PARTICULARLY DETAILS OF DOSAGE AND ADMINISTRATION, PLEASE CONSULT PRODUCT MONOGRAPH WHICH IS AVAILABLE ON REQUEST.

HOW SUPPLIED

Ca8804—Tablets SINEMET* 250, dapple-blue, oval, biconvex, scored, compressed tablets coded MSD 654, each containing 25 mg of carbidopa and 250 mg of levodopa. Available in bottles of 100 and 500.

*®Trademark

SNM-0-596-JA

PAAB CCPP

MERCK SHARP & DOHME CANADA LIMITED
P.O. BOX 1005, POINTE-CLAIRE, DORVAL H9R 4P8

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). History of melanoma or suspicious undiagnosed skin lesions.

Warnings
Discontinue levodopa therapy at least 12 hours before initiating 'Prolopa' therapy. 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.

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

Adverse reactions
Most common are abnormal involuntary movements, usually dose dependent, and 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, arrythmias 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.

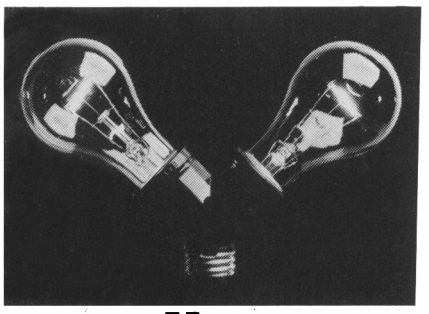
Dosage
Recommended initial dose is one capsule 'Prolopa' 100-25 once or twice daily, increased carefully by one capsule every third or fourth day until an optimum therapeutic effect is obtained without dyskinesias. At upper limits of dosage increments should be made slowly at 2 to 4-week intervals.
Optimal 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' 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 for 12 hours and initiate with 'Prolopa' 100-25 to provide approximately 15% of previous levodopa dosage. The initial daily dose, however, should not exceed 6 capsules 'Prolopa' 100-25 divided into 4 to 6 doses.

Supply
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.
Bottles of 100.
Product monograph available on request.

® Reg. Trade Mark

'Prolopa' is listed in provincial formularies. PAAB CCPP

ROCHE® Hoffmann-La Roche Limited
Vaudreuil, Québec J7V 6B3



New P Sandomigran® DS

Specific, Double Strength headache prophylaxis.

PRESCRIBING INFORMATION

SANDOMIGRAN (pizotyline)
SANDOMIGRAN D.S.

Dosage – The average maintenance dosage is 0.5 mg t.i.d. A progressive dosage is recommended until the fifth day of therapy.

The dosage range is 1 to 6 mg per day.

Since vascular headache is a paroxysmal but basically chronic disorder, treatment must extend over an adequate period of time in order to obtain maximal benefit. While some patients have responded rather quickly, most investigators agree that a four-week trial period should be instituted to determine the true efficacy of pizotyline in specific cases. The periodic nature of the disorder will have to be considered in determining when and for how long therapy should be maintained. Since some investigators have observed a change in headache pattern after several months of therapy, a drug-free interval is advisable to reassess the necessity of continuing treatment. The dosage should be reduced gradually during the last two weeks of each treatment course to avoid a "headache rebound".

Composition – Each ivory, sugar-coated tablet contains 0.5 mg of pizotyline as the hydrogen malate. Each single scored white tablet contains 1 mg of pizotyline as the hydrogen malate.

Contraindications – Anticholinergic agents, including pizotyline, are contraindicated in patients taking monoamine oxidase inhibitors and in patients with pyloroduodenal obstruction and stenosing pyloric ulcer. Pizotyline is also contraindicated for patients who have a known sensitivity to the drug. Until further studies are completed the drug is not recommended for children under the age of twelve.

Warnings and precautions – Since drowsiness may occur with pizotyline, sensitive patients should be cautioned against activities requiring rapid and precise response (*i.e. driving an automobile or* operating dangerous machinery) until their response to the drug has been determined. Since the effects of antihistamines can potentiate those of other drugs affecting the central nervous system, patients should be cautioned against drinking alcoholic beverages or taking hypnotics, sedatives, psychotherapeutic agents or other drugs with CNS depressant effects during pizotyline therapy. Administer pizotyline with caution to patients with narrow angle glaucoma or with urinary retention (e.g. prostatic hypertrophy).

Since it is desirable to keep drug administration to a minimum during pregnancy, pizotyline should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus.

Some patients developed tolerance to pizotyline with prolonged use of the drug. An increase in dosage may overcome this tolerance.

After prolonged use, hepatotoxic effects might occur and patients should be advised to report for adequate laboratory evaluation.

Patients with diabetes, cardiovascular disease and known or suspected impaired renal or hepatic function should be given pizotyline with caution, and appropriate laboratory tests should be done at regular intervals.

Lens opacities occurred in two cases but did not appear to be drug-related. However, it is recommended that any impairment in vision be reported to the attending physician for further investigation.

Side effects – Increased appetite, weight gain, and drowsiness are the most frequent side effects. An appropriate diet should be recommended by the physician for patients benefiting from the drug but gaining excessive weight. A gradual increase in the dosage of pizotyline is recommended to minimize or reduce the incidence of drowsiness. The following adverse effects have been observed less frequently in relation to the aforementioned reactions: fatigue, nausea, dizziness, headache, confusion, edema, hypotension, depression, weakness, epigastric distress, dry mouth, nervousness, impotence and muscle pain.

Supply – 0.5 mg tablets in bottles of 100 and 500; 1 mg scored tablets in bottles of 100.

Complete prescribing information available on request.

PAAB

MEMBER PMAC

SANDOZ®

Sandoz (Canada) Limited, Dorval, Quebec

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.

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.

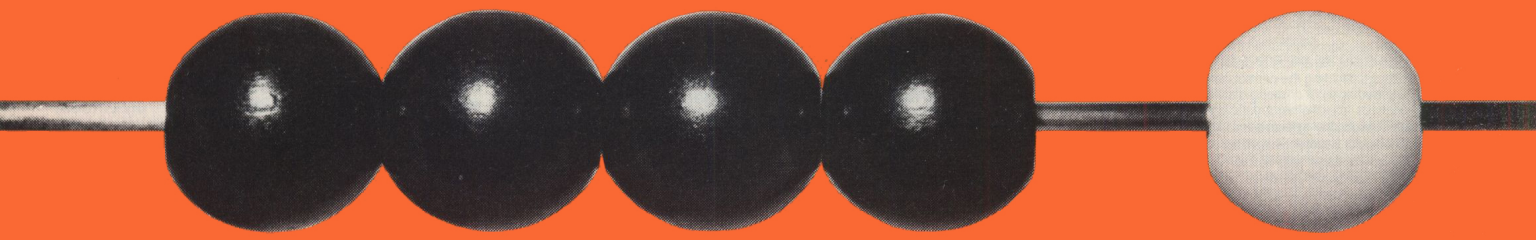
PARKE-DAVIS

PMAC

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

PAAB CCPP

the 4:1 ratio



preferred by Parkinson patients

https://doi.org/10.1017/S0317167100042748 Published online by Cambridge University Press

See page xiv for brief prescribing information.

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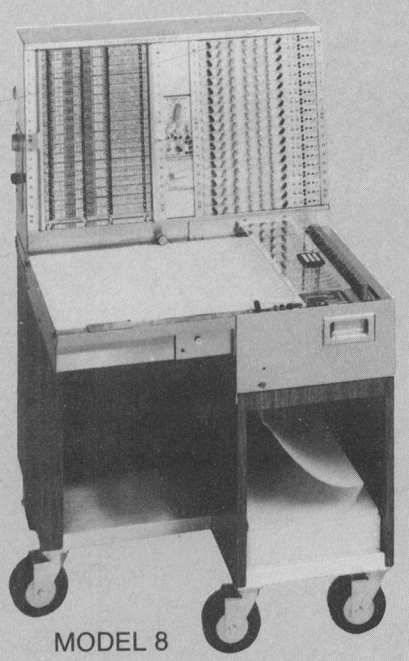
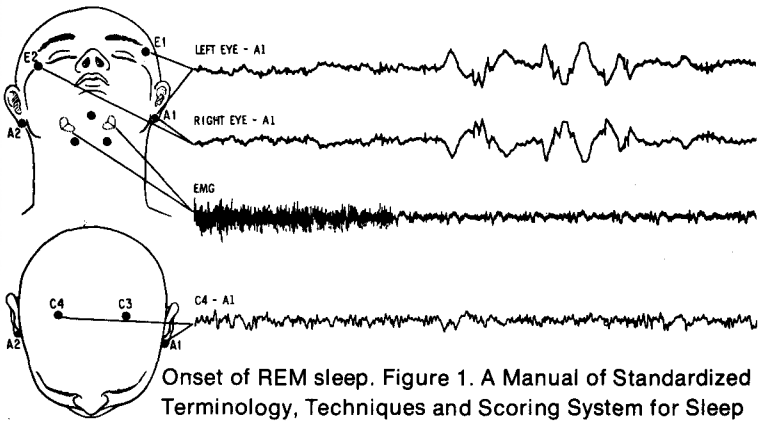
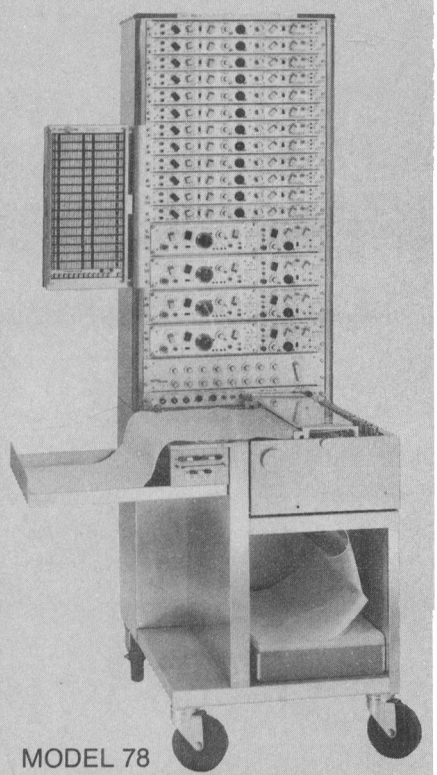


MODEL 8

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.

For dual purpose applications where the primary interest is in clinical EEG and the secondary interest involves multiple parameter sleep studies, the Model 8 EEG is the instrument of choice.

For dependable long-term studies — rely on Grass, recording bioelectric activity since 1935.

Write for further information on a system to meet your polysomnographic recording needs.

®GRASS MEDICAL INSTRUMENTS SINCE 1935

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D139H78

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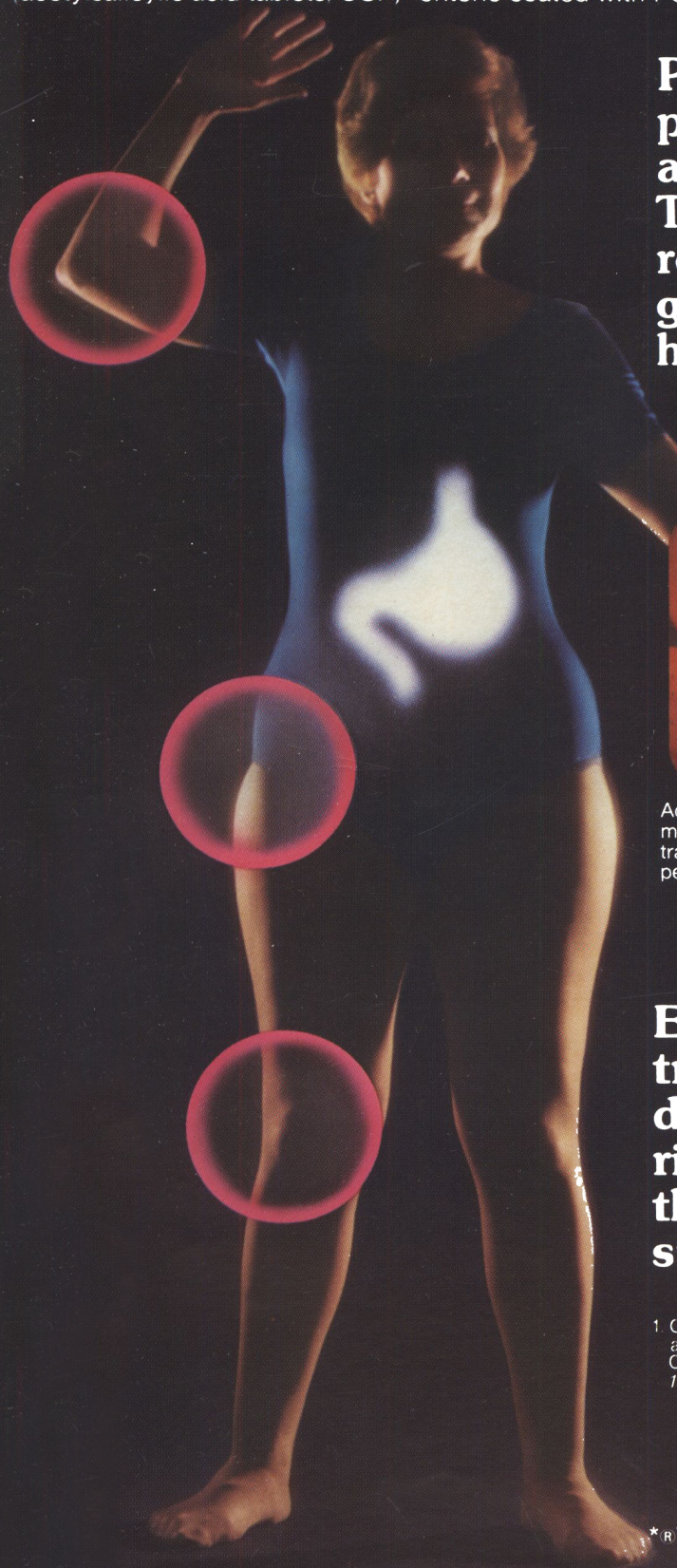
Treat arthritic pain and inflammation while reducing risk of stomach upset

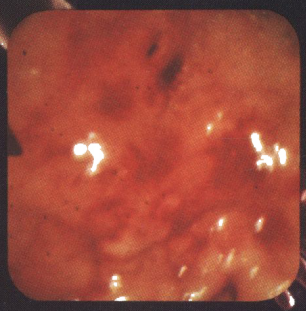
entrophen*

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



Provides therapy to relieve pain, reduce inflammation and improve mobility. The POLYMER 37* coating reduces the potential for gastric irritation due to high doses of ASA.

PLAIN ASA THERAPY



Acute erosions of gastric mucosa after oral administration of plain ASA—3.9 g per day for 14 days.[1]

THERAPY WITH ENTROPHEN*

Erosions of gastric mucosa after same regimen of ENTROPHEN*-10. Blood salicylate levels with ENTROPHEN* were comparable to ASA control.[1]

ENTROPHEN* for the treatment of arthritic disorders with reduced risk of stomach upset. It's therapy you can start with... stay with... depend on

1. Giroux, Y. et al.: The effects on the gastric mucosa of coated acetylsalicylic acid (ENTROPHEN) and of plain acetylsalicylic acid. Comparative endoscopic study. Union Médicale du Canada *106(6)*: 841-847, June 1977.

*® Trademark

Frosst

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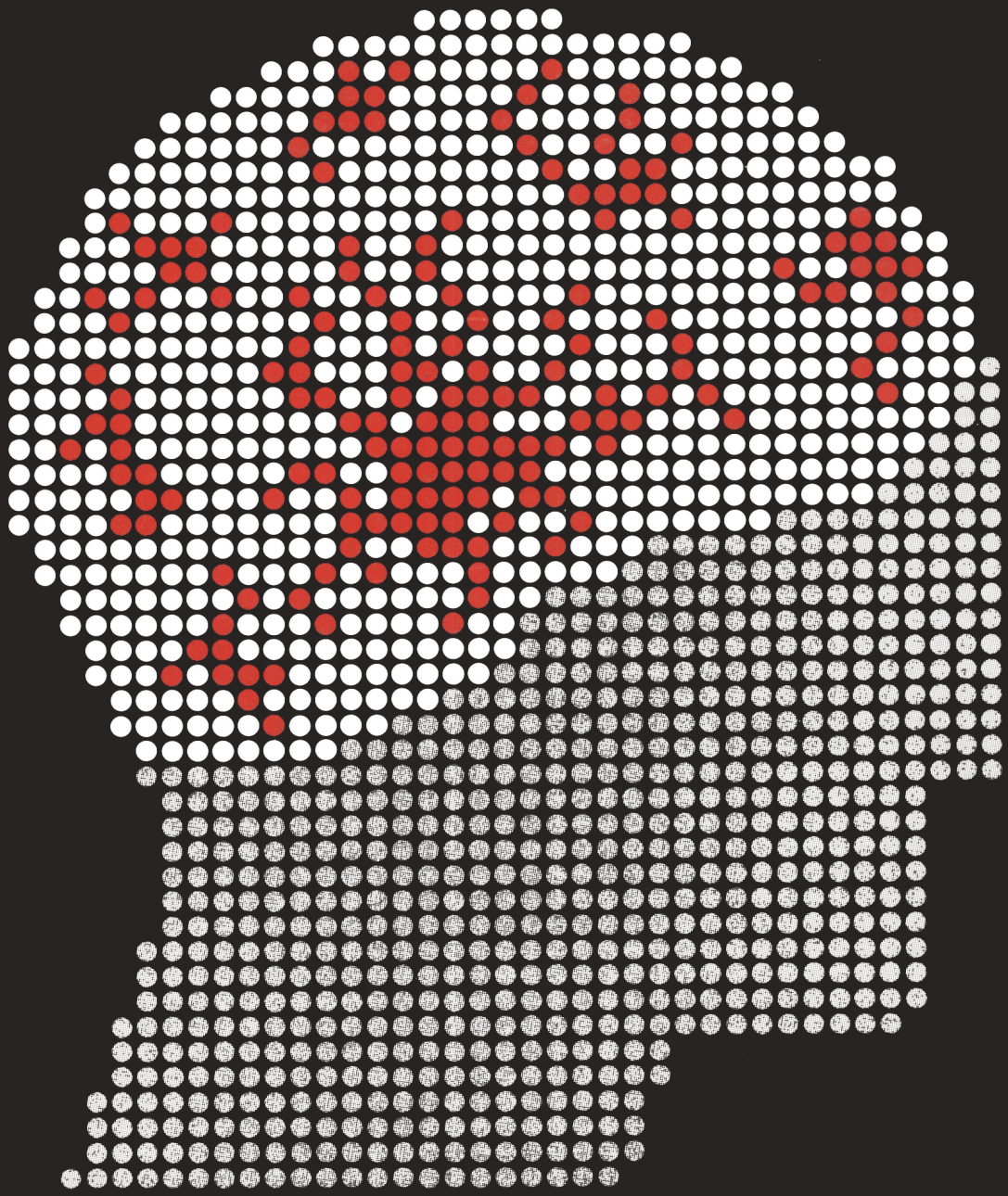
Tegretol®
carbamazepine

To help control refractory generalized tonic-clonic seizures

without excessive sedation



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Geigy

For Brief Prescribing Information see Page (xii)