

THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES

LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES

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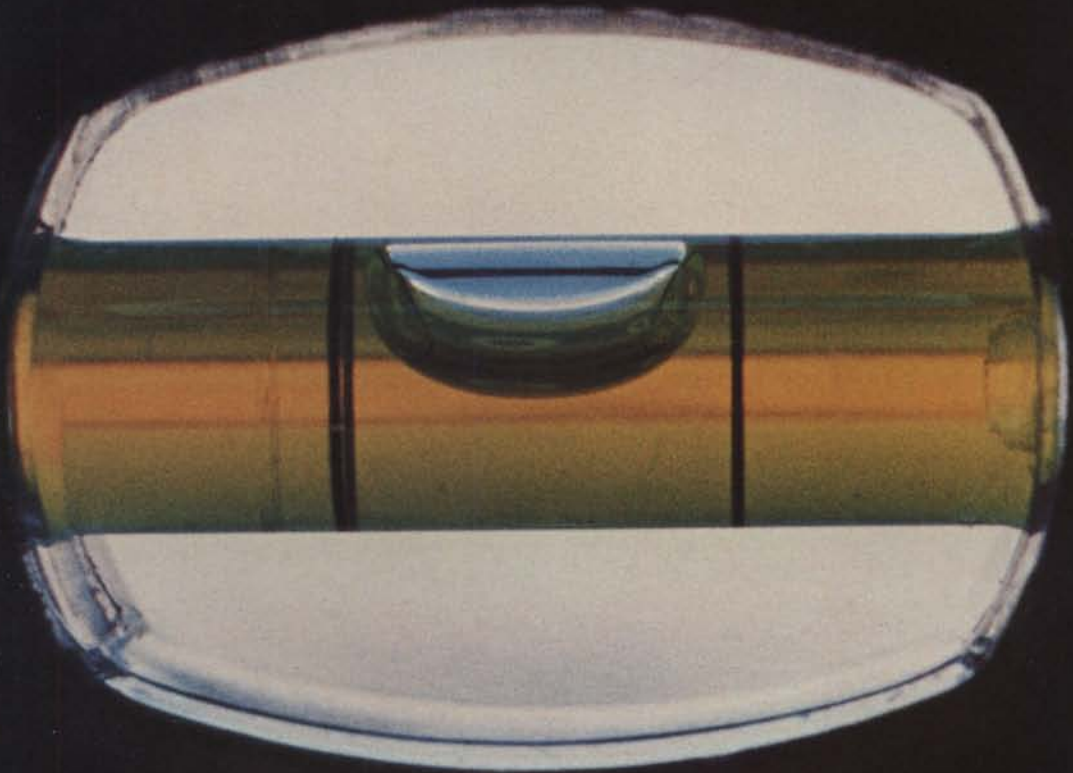
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Index to Volume 7**

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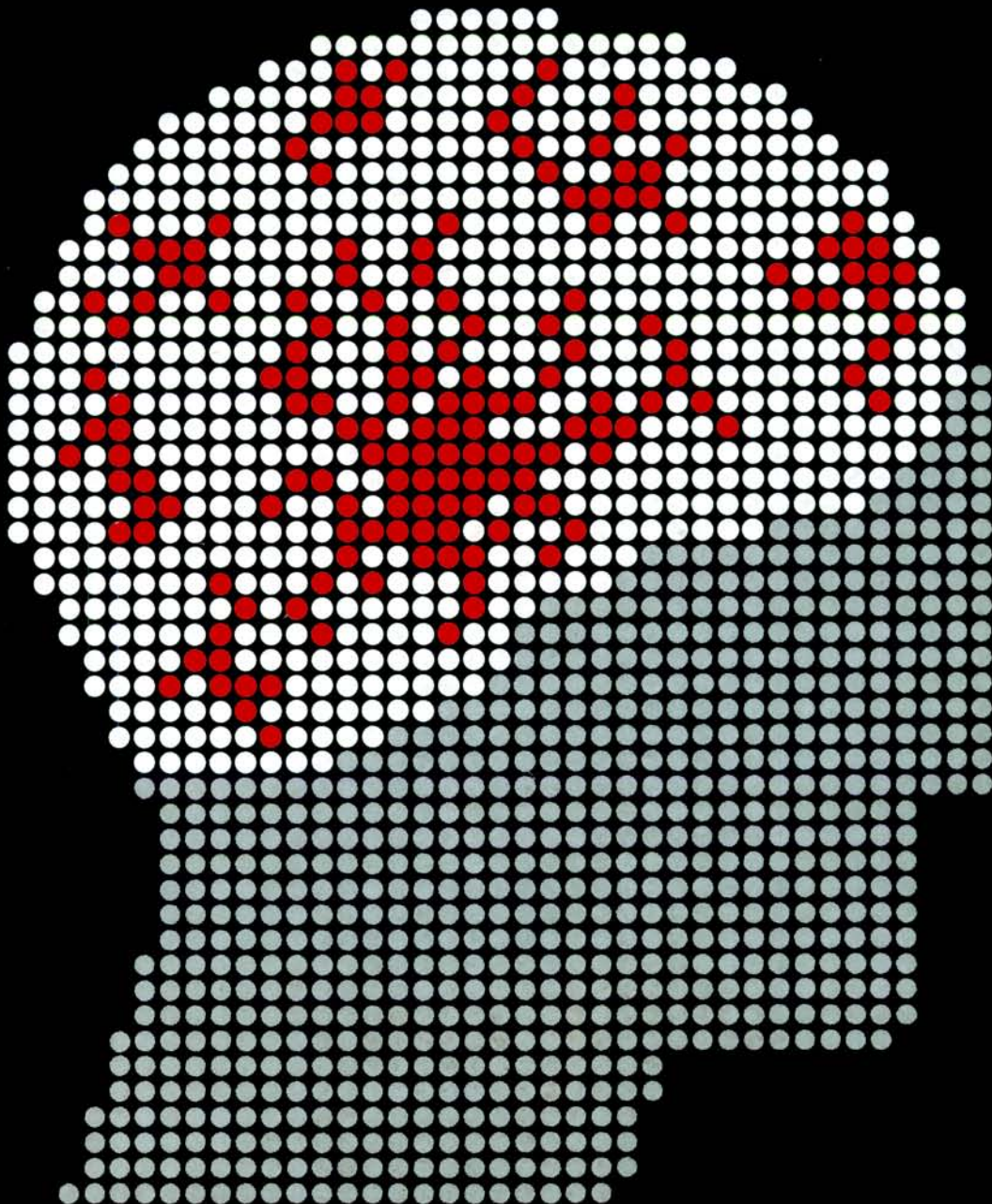
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Information see Page (V)

Brief Prescribing Information
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Indications and Clinical Use

A. Trigeminal Neuralgia:

Tegreto 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, Tegreto has relieved glossopharyngeal neuralgia. For patients who fail to respond to Tegreto, or who are sensitive to the drug, recourse to other accepted measures must be considered.

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

B. Tegreto 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.

Tegreto is essentially ineffective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge.

Contraindications

Tegreto should not be administered to patients with a history of hepatic disease or serious blood disorder. Tegreto should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer Tegreto 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 Tegreto should be low initially, and increased very gradually.

Tegreto should not be administered to patients presenting atrioventricular heart block.

Safe use in pregnancy has not been established. Therefore, Tegreto should not be administered during the first three months of pregnancy. Tegreto 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, Tegreto should not be administered to nursing mothers.

Because of the similarity of chemical structure,

Tegreto 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 Tegreto. 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 Tegreto 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, Tegreto should be immediately discontinued until the case is carefully reassessed.

Urinary Retention and Increased Intraocular Pressure: Because of its anticholinergic action, Tegreto 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 Tegreto 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: Tegreto 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 Tegreto, in order to exclude patients with atrioventricular block.

Use in Patients taking Oral Contraceptives: In women under treatment with Tegreto, 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 Tegreto, patients should be warned about the possible hazards of operating machinery or driving automobiles.

Adverse Reactions

The reactions which have been most frequently reported with Tegreto 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 Tegreto 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 Tegreto, abnormalities in liver function tests and cholestatic or hepatocellular jaundice have been observed.

Dermatological reactions: The following reactions occurred during treatment with Tegreto: 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 Tegreto 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 Tegreto 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 arrhythmias) 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 Tegreto 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 Tegreto 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 funduscopy and tonometry, are recommended.

Other reactions reported during treatment with Tegreto 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 is 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 Tegreto at intervals of not more than 3 months, depending upon the individual clinical course.

Prophylactic use of the drug in trigeminal neuralgia is not recommended. Tegreto should be taken in two or three divided doses daily, with meals whenever possible.

Dosage Forms

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

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*Reynolds, F.H. et al: Lancet, 923-926, May 1, 1976
**Goodman and Gilman, 5th Edition
***Sherwin, (1973) Arch. Neurol. (28), 178.

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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 PHELANITIN are used, it should be borne in mind that phenobarbital may cause drowsiness, and may be habit-forming. PHELANITIN, because of the methamphetamine content, should be given cautiously to patients with hypertension.

PHELANITIN 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.

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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 psychological 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.

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These minors are victims



Jean — myoclonic seizures



Michael — akinetic seizures



Carol — Lennox-Gastaut syndrome

These children, victims of minor motor seizures, may benefit from the many advantages offered by 'Rivotril'.

- Effective in reducing the frequency and/or severity of a variety of epileptic seizures
 - akinetic seizures
 - myoclonic seizures
 - Lennox-Gastaut syndrome (petit mal variant)
 - absence seizures (where succinimide therapy has failed)
- flexible dosage regimen encourages patient compliance
- no reports of incompatibility with a ketogenic diet
- economical, for long-term therapy
- may be used concomitantly with most other anticonvulsants

'Rivotril' has not been associated with the severe side effects seen with some other anticonvulsant medications.

- No reports of serious side effects, such as hepatotoxicity.
- Very low incidence of nausea and G.I. upsets.¹
- No serious problems of drug interaction. (eg. ASA)
- Proven safety record in long-term administration.
- Drowsiness, which may occur, is generally dose-related and may be well controlled with proper dosage adjustment.^{2,3}



For Rx Summary, see page xviii

Rivotril[®] for the victims of minor motor seizures

New Vira-A Parenteral



Reduces the Mortality Rate Caused by Herpes Simplex Encephalitis from 70% to 28%.

Vira-A Parenteral, a major new development from Parke-Davis Research, significantly reduces the mortality rate of patients with herpes simplex encephalitis.

In controlled studies, Vira-A Parenteral (vidarabine for infusion) reduced the mortality rate caused by herpes simplex encephalitis from 70% to 28%. Over 50% of treated survivors had no or only moderately debilitating neurologic sequelae. (1)

Additional evidence suggests that Vira-A Parenteral prevents the reproduction of herpes simplex without substantial interference with the normal function of the patient's own cells. (2)

All hospital pharmacies have been provided with full prescribing information. If further information is required, contact the Medical Director, Parke, Davis and Company, Ltd.

PARKE-DAVIS

Vir-a-A
(Sterile Vidarabine for Infusion)

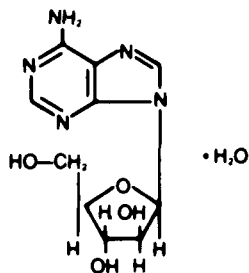
**THERAPEUTIC OR
PHARMACOLOGICAL CLASSIFICATION**
Antiviral Agent

**STRUCTURAL FORMULA
AND CHEMISTRY**

Molecular Formula: C₁₀H₁₃N₅O₄·H₂O

Molecular Weight: 285.2

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



Description: Vir-a-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. Vir-a-A, an antiviral drug, is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vir-a-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, Vir-a-A inhibits viral DNA synthesis.

Excretion of Vir-a-A is principally via the kidneys. Vir-a-A is rapidly deaminated to Ara-Hx (arabinoxylhypoxanthine), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is significantly less than Vir-a-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 Vir-a-A and Ara-Hx is attained by day 3 following the first infusion. The urinary excretion rate of Vir-a-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. Vir-a-A is indicated in the treatment of Herpes Simplex virus encephalitis. Controlled studies indicate that Vir-a-A therapy reduced the mortality rate due to Herpes Simplex virus encephalitis from 70 to 28%.

Vir-a-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 Vir-a-A for infusion is effective in the management of encephalitis due to varicella-zoster or vaccinia viruses. Vir-a-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 Vir-a-A against cytomegalovirus, vaccinia virus, or smallpox virus.

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

Warnings. Vir-a-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 Vir-a-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 Vir-a-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 Vir-a-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 Vir-a-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 Vir-a-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 Vir-a-A to achieve clinical response.

Usage in Pregnancy. Vir-a-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. Vir-a-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 Vir-a-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 Vir-a-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, Vir-a-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 Vir-a-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 Vir-a-A, due to its low solubility. Doses of Vir-a-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, 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 LD₅₀ for Vir-a-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 Vir-a-A per ml of suspension. The solubility of Vir-a-A in intravenous infusion fluids is limited. Each one mg of Vir-a-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 Vir-a-A.

The following intravenous infusion fluids are compatible with Vir-a-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 Vir-a-A well to obtain a homogeneous suspension before measuring and transferring.

Prepare the Vir-a-A solution for intravenous administration by aseptically transferring the proper dose of Vir-a-A into an appropriate intravenous infusion fluid. The intravenous infusion fluid used to prepare the Vir-a-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. Vir-a-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 LD₅₀ for Vir-a-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 LD₅₀ value. The hepatic megalocytosis appeared to regress over several months. Acute intravenous LD₅₀ values could not be obtained because of the limited solubility of Vir-a-A.

Subacute Toxicity. Rats, dogs, and monkeys have been given daily intramuscular injections of Vir-a-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 Vir-a-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 Vir-a-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

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Scarborough, Ontario M1K 5C5

New Lior

baclofen

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



Acts primarily at the spinal level

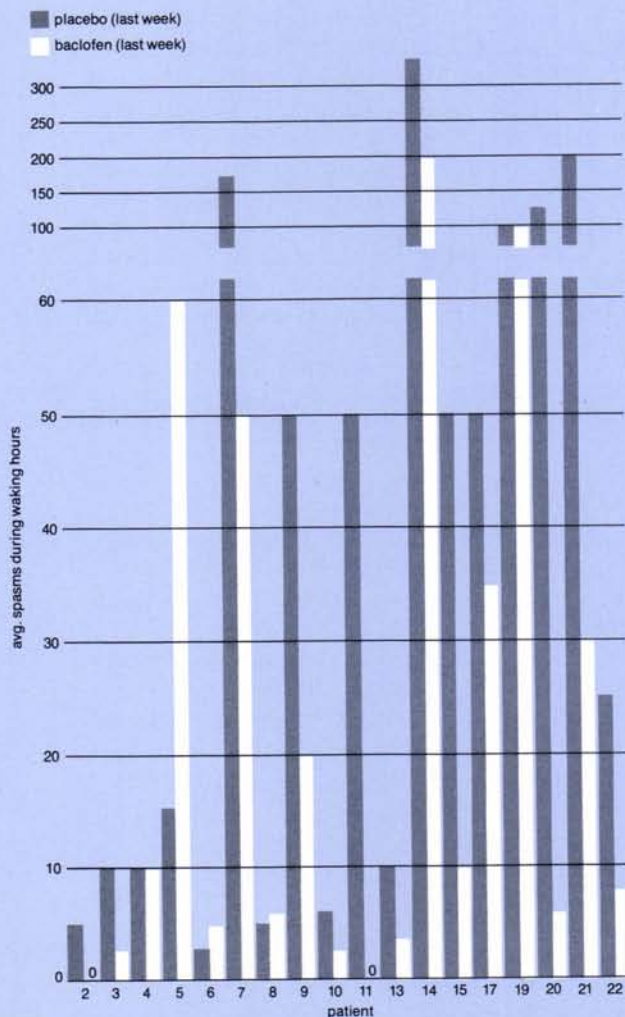
Lioresal is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of the afferent terminals. However, the precise mechanism of action is not fully known. Actions at supraspinal sites may also occur and contribute to the clinical effect.

esal[®]

Effective

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

Figure 1. Average daily number of spasms during the last week of baclofen and placebo treatment periods in the 18 patients with spontaneous daytime spasms. (From Duncan et al¹)



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

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

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

Facilitates physical therapy

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

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

Effect of treatment on resistance to passive movement (Adapted from Duncan et al¹)

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

Geigy

For Brief Prescribing Information, see page xiv. G-9038-R

Lioresal® baclofen

Brief Prescribing Information

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 child-bearing 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).

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. Duncan, G. N., Shahani, B. T., and Young, R. R.: An evaluation of baclofen treatment for certain symptoms in patients with spinal cord lesions. *Neurology*, (May) 1976, pp. 441-446.
2. Jones, R. F.: *Lioresal in the control of spasticity*. Spasticity... A topical survey, Hans Huber Publishers, Bern, 1972, P. 113.
3. McLellan, D. L.: Effects of baclofen upon monosynaptic and tonic vibration reflexes in patients with spasticity. *J. Neuro. Neurosurg. Psychiatry*, 36(4): 555-560, (Aug.) 1973.

Geigy Dorval, Qué. H9S 1B1



G-9038-R

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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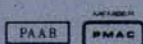
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sign of attack.

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The Canadian Journal of Neurological Sciences is the official publication of the Canadian Neurological Society, the Canadian Neurosurgical Society and the Canadian Society of Electroencephalographers, and Electromyographers and Clinical Neurophysiologists.

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

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

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