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The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology
XVII Canadian Congress of Neurological Sciences
June 23 - 26, 1982 Toronto, Ontario

VOLUME 9, NO. 1 FEBRUARY 1982

SERC®

(betahistine hydrochloride tablets)

For the management of Vertigo

■ Proven efficacy

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

■ Restores vestibular responses

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

■ Reduced severity of episodic vertigo

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

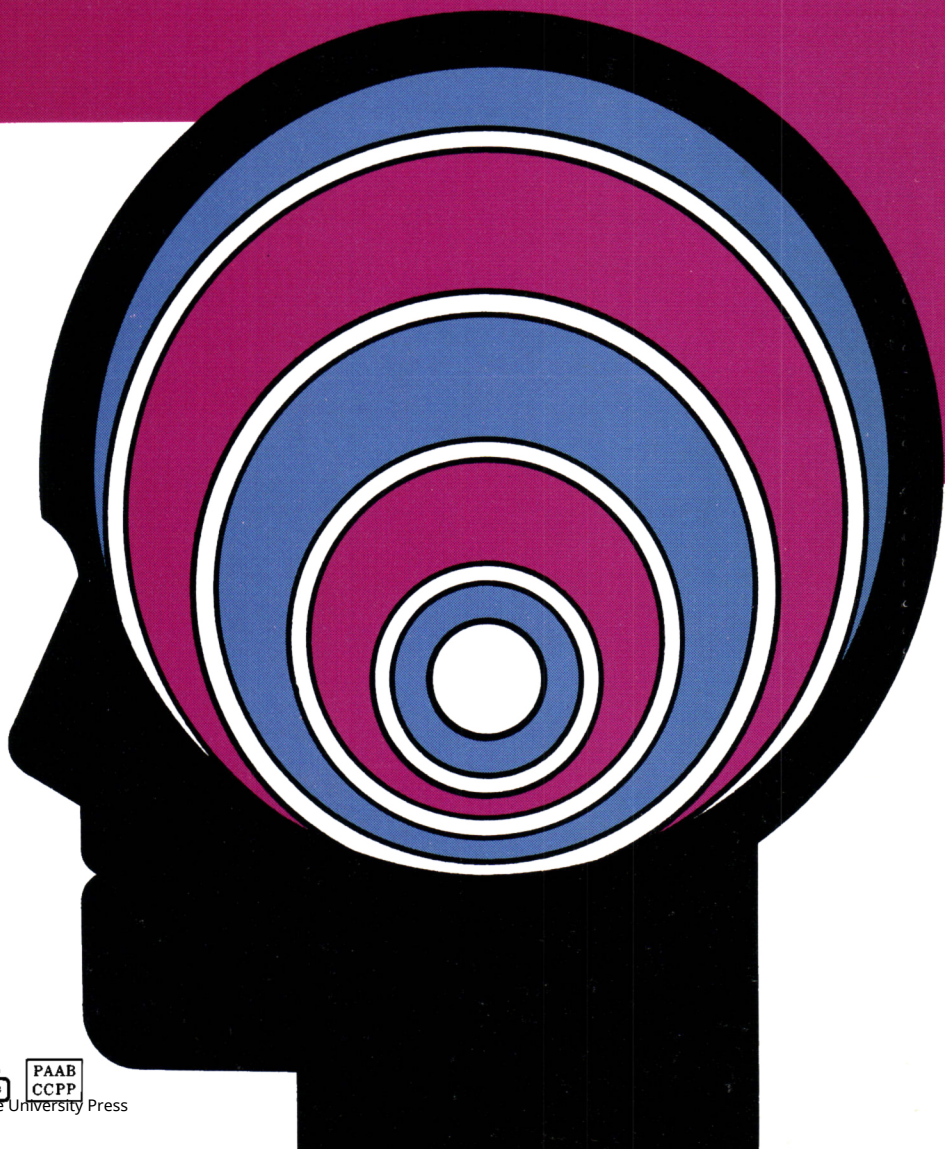
■ Well tolerated

"No adverse reactions were observed."[1]

REFERENCES:

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

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



PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

Full prescribing information available on request.

UNIMED Canada Inc.

Dorval, Québec H9P 2P4

MEMBER PMAC PAAB CCPP

DILANTIN*

Extended Phenytoin Sodium Capsules U.S.P.

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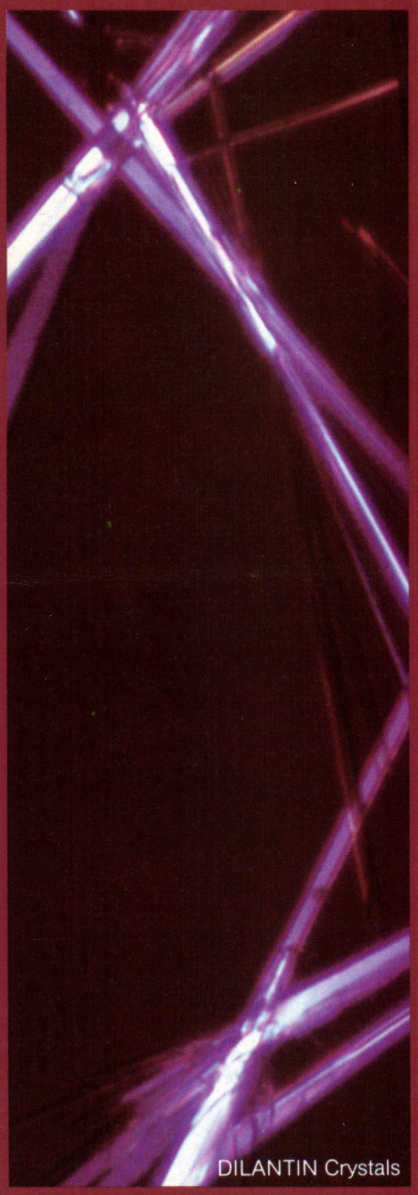

DILANTIN Crystals

USP XX now differentiates between Extended and Prompt Phenytoin Sodium Capsules.

Extended phenytoin sodium has been recognized as a distinct pharmaceutical entity. Its slow dissolution and absorption do not create significant fluctuations in phenytoin blood levels.

Prompt phenytoin sodium has a faster dissolution and higher initial blood levels. The two forms of phenytoin sodium are **not interchangeable**.**

DILANTIN Capsules have not changed.

Extended effect has always been the action of DILANTIN therapy. Only the U.S.P. standards have changed to recognize the difference between "extended" and "prompt" phenytoin sodium. Both you and your patient can continue to benefit from the consistent antiepileptic action of DILANTIN capsules.

Once-daily-dosage option is confirmed for DILANTIN Capsules.

Extended action of DILANTIN offers greater **convenience and improved patient compliance**. Dependable, effective therapy is now available through a once-daily-dosage option, once seizure control has been established with divided doses.

DILANTIN formulation ensures dependable bioavailability.

Extended phenytoin classification of DILANTIN capsules is the result of its unique dissolution profile. Due to its **special formulation**, DILANTIN exerts a slow, steady release of phenytoin for **dependable bioavailability.**

**Patients should be maintained on one form of phenytoin (extended or prompt) to avoid toxicity or loss of seizure control.

START WITH DILANTIN–STAY WITH DILANTIN FOR OVER A GENERATION, THE STANDARD IN EPILEPSY MANAGEMENT

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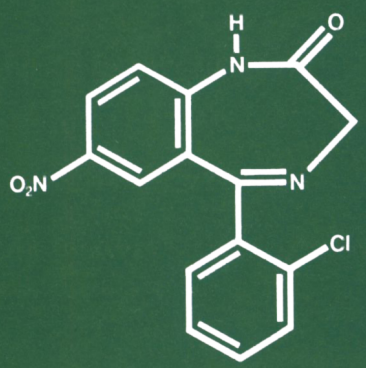
The Roche® spectrum of anticonvulsants

Rivotril®

(clonazepam)

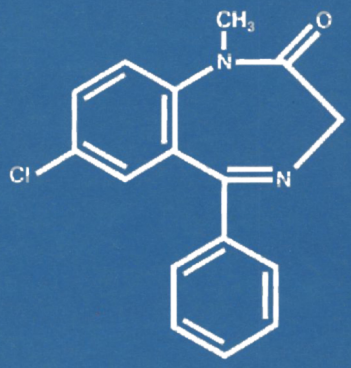


Indications:
Myoclonic and Akinetic Seizures
Petit Mal Variant
(Lennox-Gestaut)
Petit Mal
(refractory to succinimides)

Availability:
0.5 mg and 2 mg tablets

Valium® Roche® injectable

(diazepam)

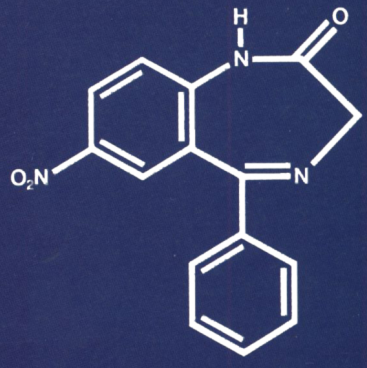


Indications:
Status Epilepticus
Severe Recurrent Seizures

Availability:
5 mg/ml in 2 ml ampoules

Mogadon®

(nitrazepam)



Indications:
Myoclonic Seizures

Availability:
5 mg and 10 mg tablets

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Available on Request

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We took a good idea and doubled it.

Now you have new strength to fight migraine. New Sandomigran DS is simple, effective headache prophylaxis which encourages good compliance.

For patients who overuse or are refractory to analgesics or ergotamine – choose the strong one, Sandomigran DS.

New Sandomigran DS

(Double Strength 1 mg tablets)

Specific, Double Strength headache prophylaxis.

Dosage range: 1 to 6 tablets/day in divided doses

SANDOZ

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

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

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

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

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

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

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

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

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

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

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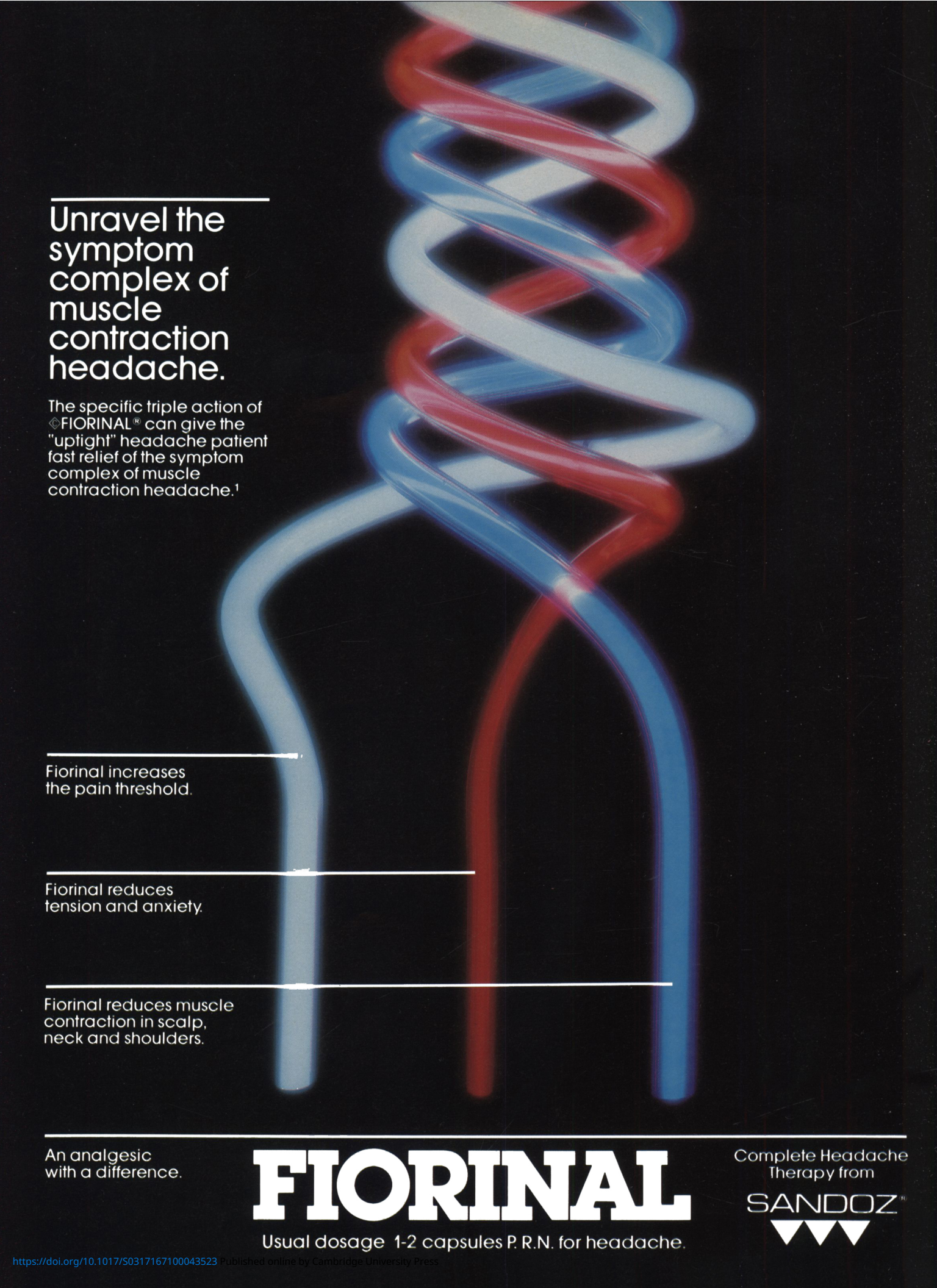

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Brief Prescribing Information

℞ **Lioresal**® baclofen

Action

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

Indications and Clinical Uses

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

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

Contraindications

Hypersensitivity to **Lioresal** (baclofen).

Warnings

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

Precautions

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

Adverse Reactions

The most common adverse reactions associated with **Lioresal** (baclofen) are transient drowsiness, dizziness, weakness and fatigue. Others reported: *Neuropsychiatric:* Headache (<10%), insomnia (<10%), and, rarely, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizures. *Cardiovascular:* Hypotension (<10%), rare instances of dyspnea, palpitation, chest pain, syncope. *Gastrointestinal:* Nausea, (approx. 10%), constipation (<10%), and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool. *Genitourinary:* Urinary frequency (<10%), and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria. *Other:* Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion. Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

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

Symptoms and Treatment of Overdosage

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

Dosage and Administration

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

The following dosage titration schedule is suggested:

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

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).

Availability: Lioresal (baclofen) 10 mg tablets. *Description:* White to off-white flat-faced, oval tablets with Geigy monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side. Available in bottles of 100 tablets.

References:

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

Product monoraph supplied on request.

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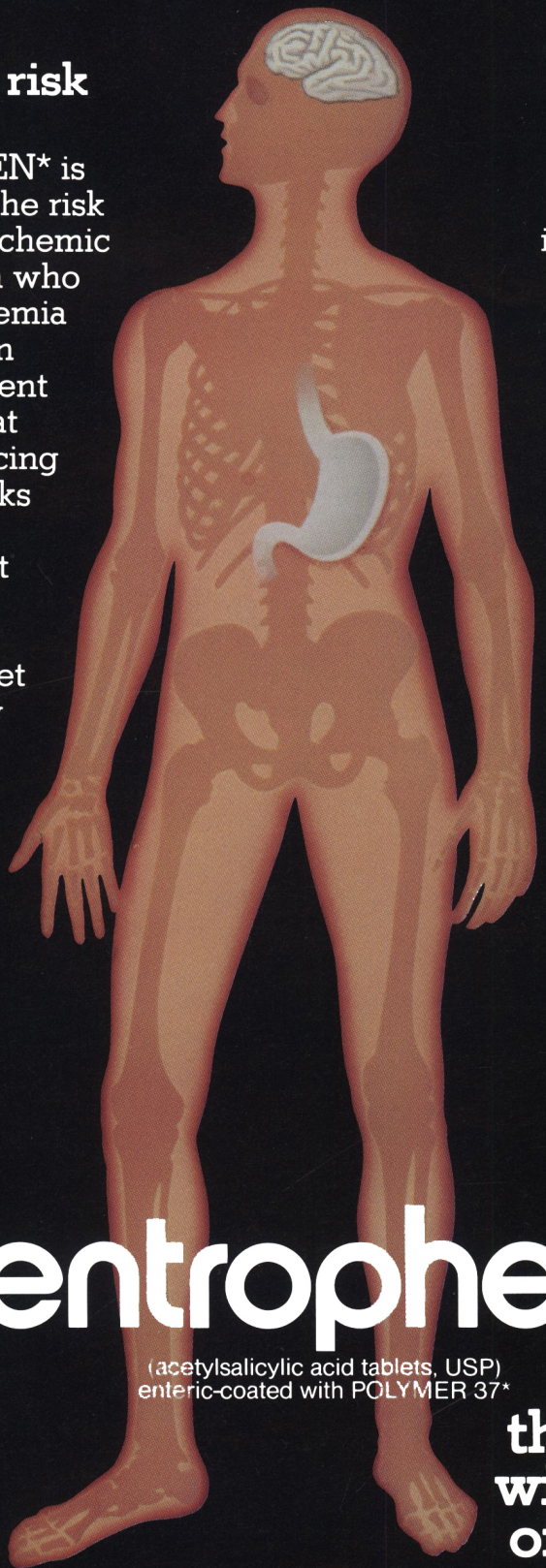
NOW IN STROKE

The Advantages of ENTROPHEN*

To reduce the risk of stroke

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

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



with reduced risk of stomach upset

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

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

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

entrophen*

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

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

Frosst
CHARLES E. FROSST & CO.

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

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TABLETS

entrophen*

(acetylsalicylic acid tablets, USP)

Enteric-coated with POLYMER 37*

Anti-Inflammatory—Analgesic Agent

Platelet Aggregation Inhibitor

DESCRIPTION

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

ACTION

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

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

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

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

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

INDICATIONS

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

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

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

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

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

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

CONTRAINDICATIONS

Sensitivity to the ingredients
Active peptic ulcer

Patients who had a bronchospastic reaction to ASA or non-steroidal anti-inflammatory drugs.

WARNINGS

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

PRECAUTIONS

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

Salicylates can produce changes in thyroid function tests.

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

Use in Pregnancy

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

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

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

Drug Interactions

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

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

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

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

Salicylates also retard the renal elimination of methotrexate.

ADVERSE REACTIONS

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

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

Treatment

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

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

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

DOSAGE AND ADMINISTRATION

Analgesic; antipyretic

Up to 2.925 g daily as necessary.

Anti-Inflammatory

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

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

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

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

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

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

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

Rheumatic Fever

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

Cerebral Ischemic attacks (men)

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

AVAILABILITY

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

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

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

FULL PRODUCT MONOGRAPH AVAILABLE ON REQUEST.

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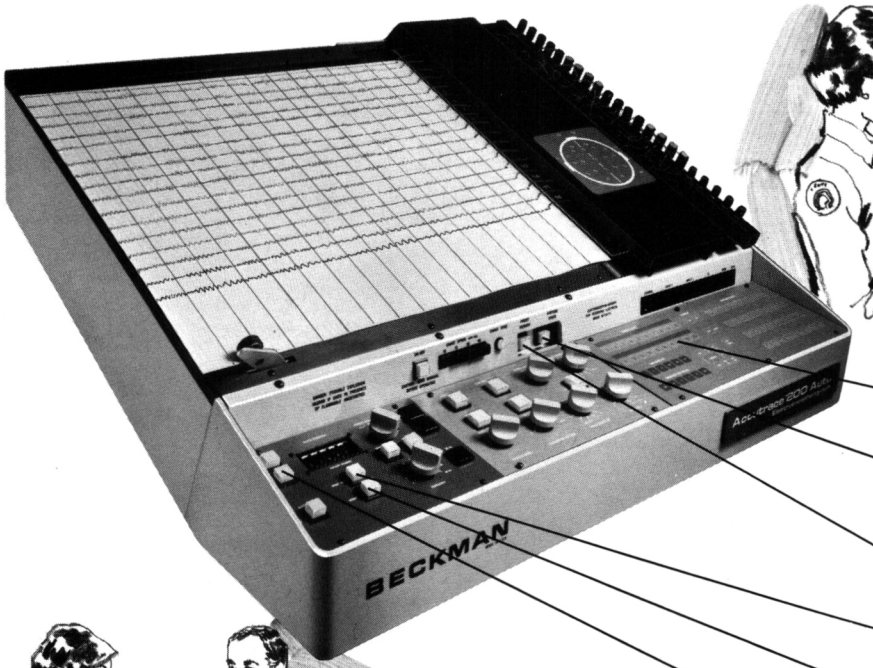

Touch control panel for fast, quiet entry of override electrodes, sensitivity and other functions

Exclusive automated self-diagnostic systems check

Exclusive programmable presets—reprogram any preset at any time, in seconds—build your own "library" of specific presets for specific applications

Exclusive automated imprinting of patient ID and preset numbers by top event marker

Exclusive autoverification of filter settings and sensitivity controls

Exclusive auto-run for automated sequencing and progression of preset montages

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First, the Technician has more time than ever before to devote to caring for the patient. This is exceptionally important when dealing with difficult or confused subjects.

Second, the instrument being used is an Accutrace model 200A.

Presets can be adjusted immediately at the touch of a button to correspond to the patient's current condition. A remote marker lets you flag important events on the record... even while you are at the patient's bedside.

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To receive further information on the Accutrace 200A, our acclaimed EEG Workshops, or the financial alternatives to a cash purchase, just call (312) 671-3300 *collect*, or mail this coupon today.

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- ☐ The Accutrace model 200A EEG
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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

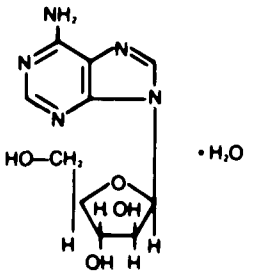
Vira-A

(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.

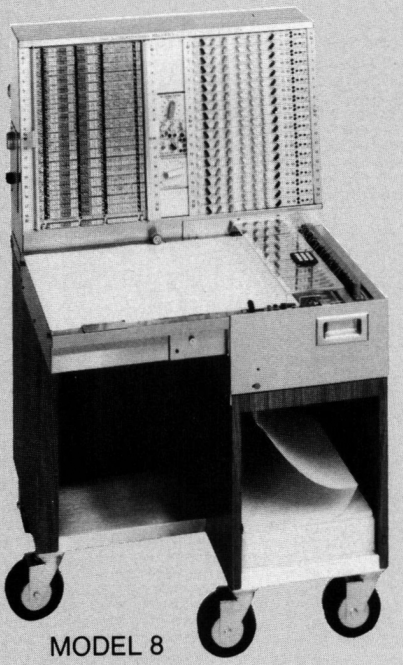
Hepatic megalocytosis, associated with vidarabine treatment, has been found in short- and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.

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.

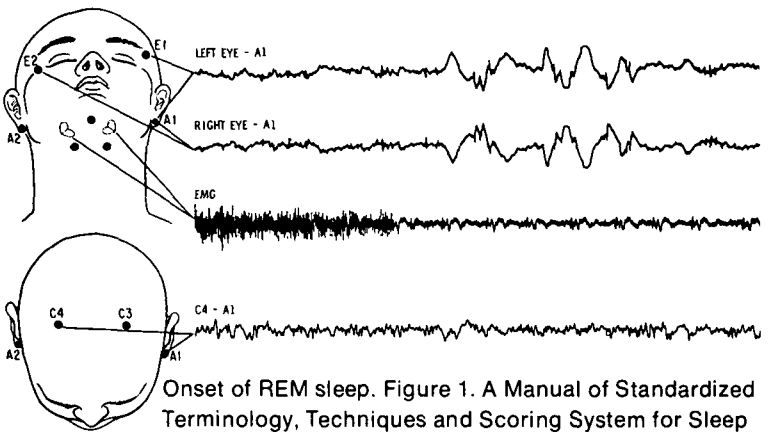
PARKE-DAVIS

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

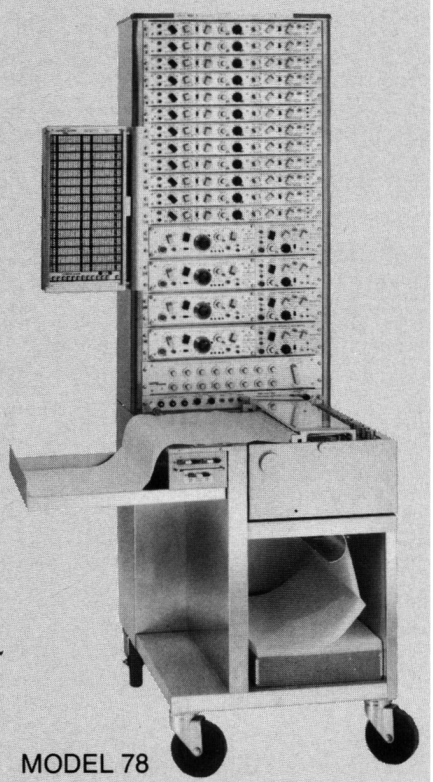


MODEL 8

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.

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