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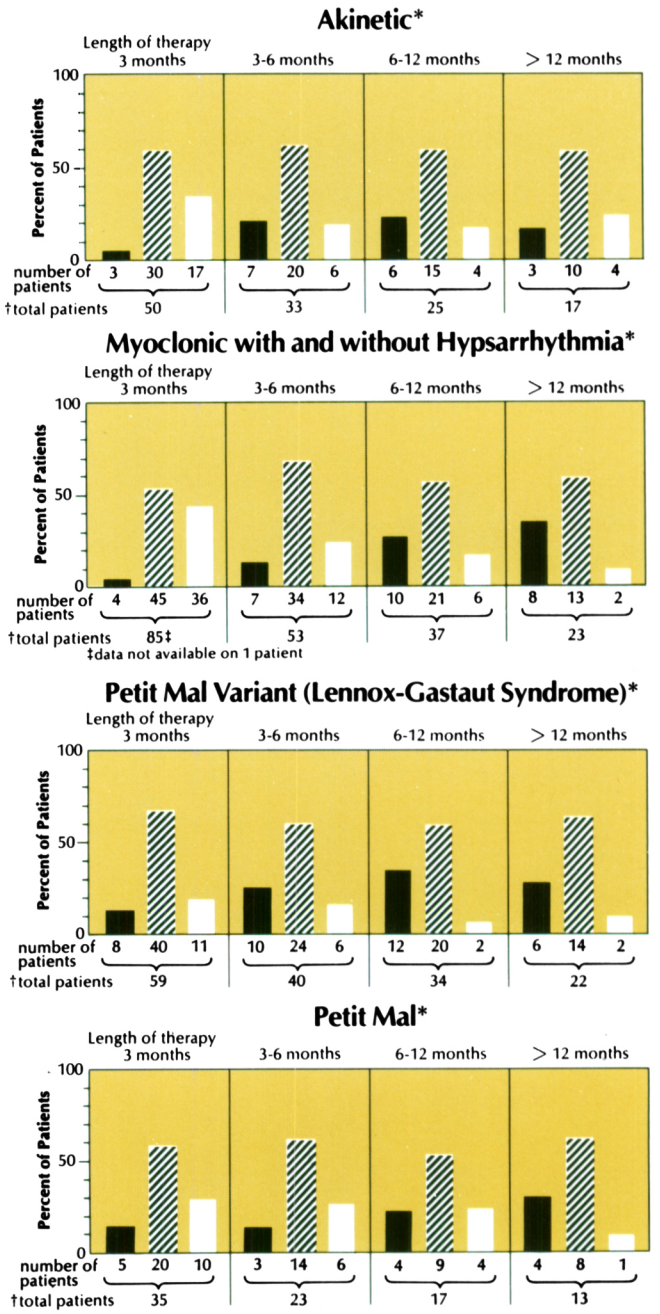
Rivotril®

a new oral anticonvulsant from 'Roche' research

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

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

Effect of RIVOTRIL on seizure frequency



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

*Data on file, Hoffmann-La Roche Limited

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

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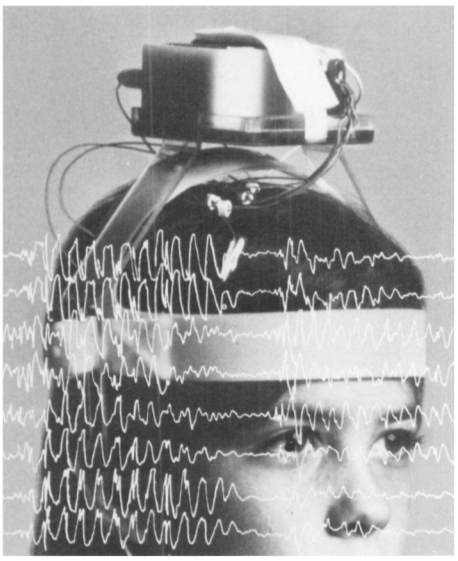
An important aid in the management of minor seizures



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

Rivotril® (clonazepam)

Brief Prescribing Information

Action

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

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

Indications

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

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

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

Contraindications

In patients with:

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

Warnings

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

Mothers receiving RIVOTRIL should not breast feed their infants.

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

Precautions

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

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

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

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

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

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

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

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

Adverse reactions

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

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

Dosage and administration

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

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

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

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

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

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

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

Supply

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

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Tegretol®
Carbamazepine

Brief prescribing information
Tegretol® 200 mg
Carbamazepine

Indications and clinical use
A. Trigeminal Neuralgia:
Tegretol is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, Tegretol has relieved glossopharyngeal neuralgia. For patients who fail to respond to Tegretol, or who are sensitive to the drug, recourse to other accepted measures must be considered.

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

B. Tegretol has been found useful in:

1) 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.

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.

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.

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.

Driving and Operating Hazardous Machinery:
Because dizziness and drowsiness are possible side effects of Tegretol, 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 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 sensitivitiy 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, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications have resulted in fatalities.

Other cardiovascular complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds. Whether all these complications are drug-related is not known at this time.

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 slit-lamp 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 psychomotor and other secondary or partial seizures:
A low initial daily dosage with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

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 ben 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 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 recommended.

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, single-scored tablet, engraved with Geigy signet.

Availability
Bottles of 50 and 500 tablets. Protect from moisture.

References

1. Livingston, S.: "Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence". Springfield, Charles C. Thomas, 1972

2. Braunhofer, J.: Med Klin. 60: 343-348, 1965

Lerman, P., and Kivity-Ephraim, S.: Carbamazepine Sole Anticonvulsant for Focal Epilepsy of Childhood. Epilepsia, 15: 229-234, 1974, New York

Full information is available on request.

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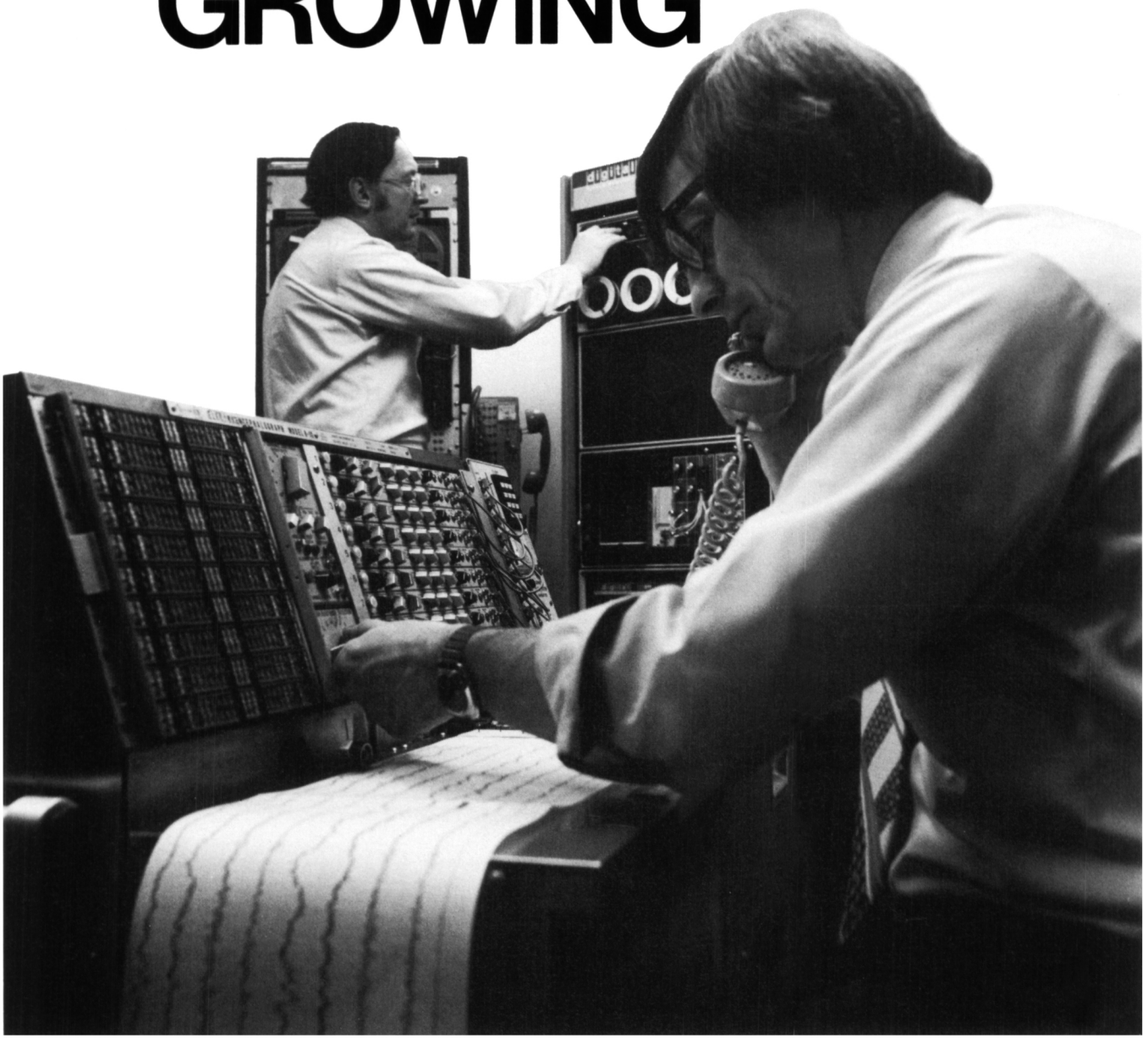

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A continuing Medical Educational Program entitled "Seizure Disorders: Diagnosis and Clinical Management" (consisting of 2 cassette tape recordings and 200 35-mm slides) is available from Parke-Davis. Please contact your Parke-Davis representative for availability.

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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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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.

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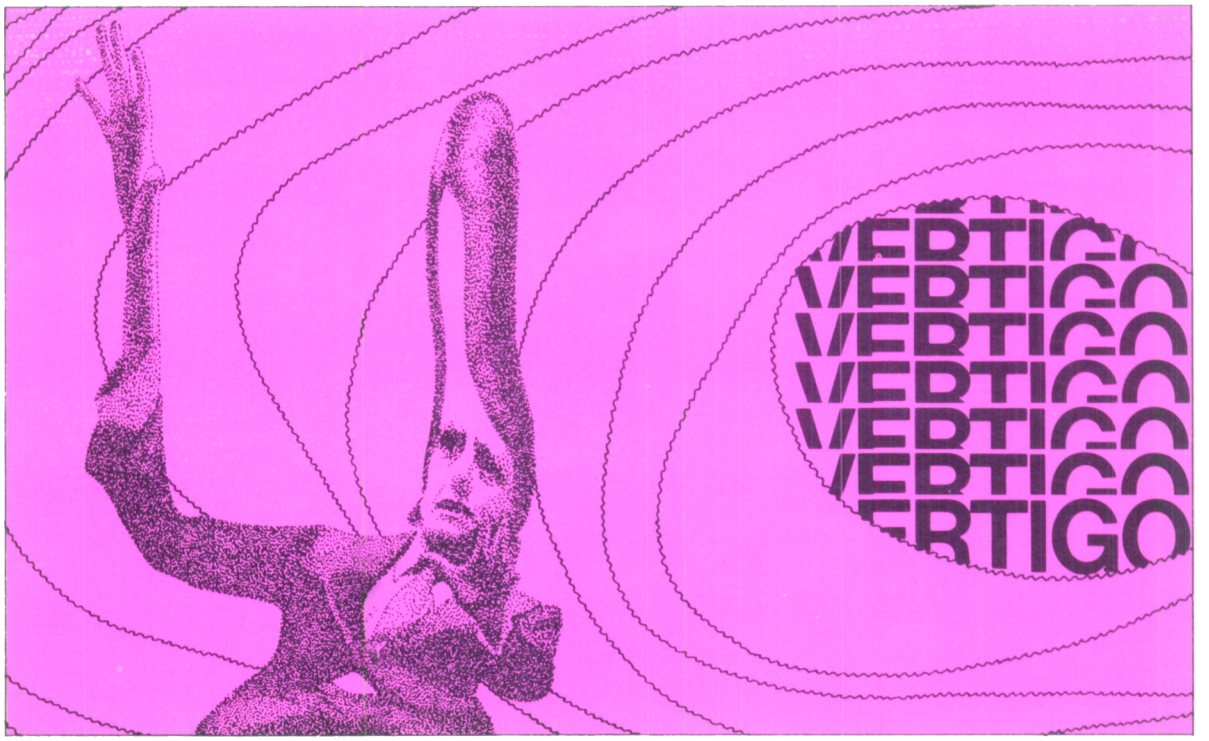
For the management of Vertigo in Meniere's disease



SERC®

(Betahistine hydrochloride) TABLETS

A decade of clinical success in Canada

Chemically Unique Vasoactive Compound

- Vascular responses similar to those of histamine[1, 2]
- Tends to restore, not depress vestibular response[3, 4]

May Increase Blood Flow To Inner Ear

- Increases cochlear blood flow in experimental animals[5, 6]
- Increases basilar and labyrinthine artery flow in canine studies[7, 8]

Demonstrated Efficacy and Patient Acceptance

- Reduces the number and severity of vertigo attacks[9, 10]
- Suitable for long term management[9, 10]
- Effective when other medications failed[9, 10]
- Well tolerated[2, 3, 4, 9, 10]

histaminic – not antihistaminic often a more helpful approach

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PRESCRIBING INFORMATION

DESCRIPTION AND CHEMISTRY: SERC is the proprietary name for a histamine-like drug generically designated as betahistine hydrochloride.
INDICATIONS: SERC may be of value in reducing the episodes of vertigo in Meniere's disease. No claim is made for the effectiveness of SERC in the symptomatic treatment of any form of vertigo other than that associated with Meniere's disease.
DOSAGE AND ADMINISTRATION: The usual adult dosage has been one to two tablets (4 mg. each) administered orally three times a day.
Recommended starting dose is two tablets three times daily. Therapy is then adjusted as needed to maintain patient response. The dosage has ranged from two tablets per day to eight tablets per day. No more than eight tablets are recommended to be taken in any one day.
SERC (betahistine hydrochloride) is not recommended for use in children. As with all drugs, SERC should be kept out of reach of children.
CONTRAINDICATIONS: Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using SERC. Although no causal relation has been established SERC is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. SERC is also contraindicated in patients with pheochromocytoma.
PRECAUTIONS: Although clinical intolerance to SERC by patients with bronchial asthma has not been demonstrated, caution should be exercised if the drug is used in these patients.
USE IN PREGNANCY: The safety of SERC in pregnancy has not been established. Therefore, its use in pregnancy or lactation, or in women of childbearing age requires that its potential benefits be weighed against the possible risks.
ADVERSE REACTIONS: Occasional patients have experienced gastric upset, nausea and headache.
HOW SUPPLIED: Scored tablets of 4 mg. each in bottles of 100 tablets.

Full Prescribing Information available on request.

UNIMED Pharmaceuticals Limited
Dorval, Québec, H9P 2P4

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CCPP

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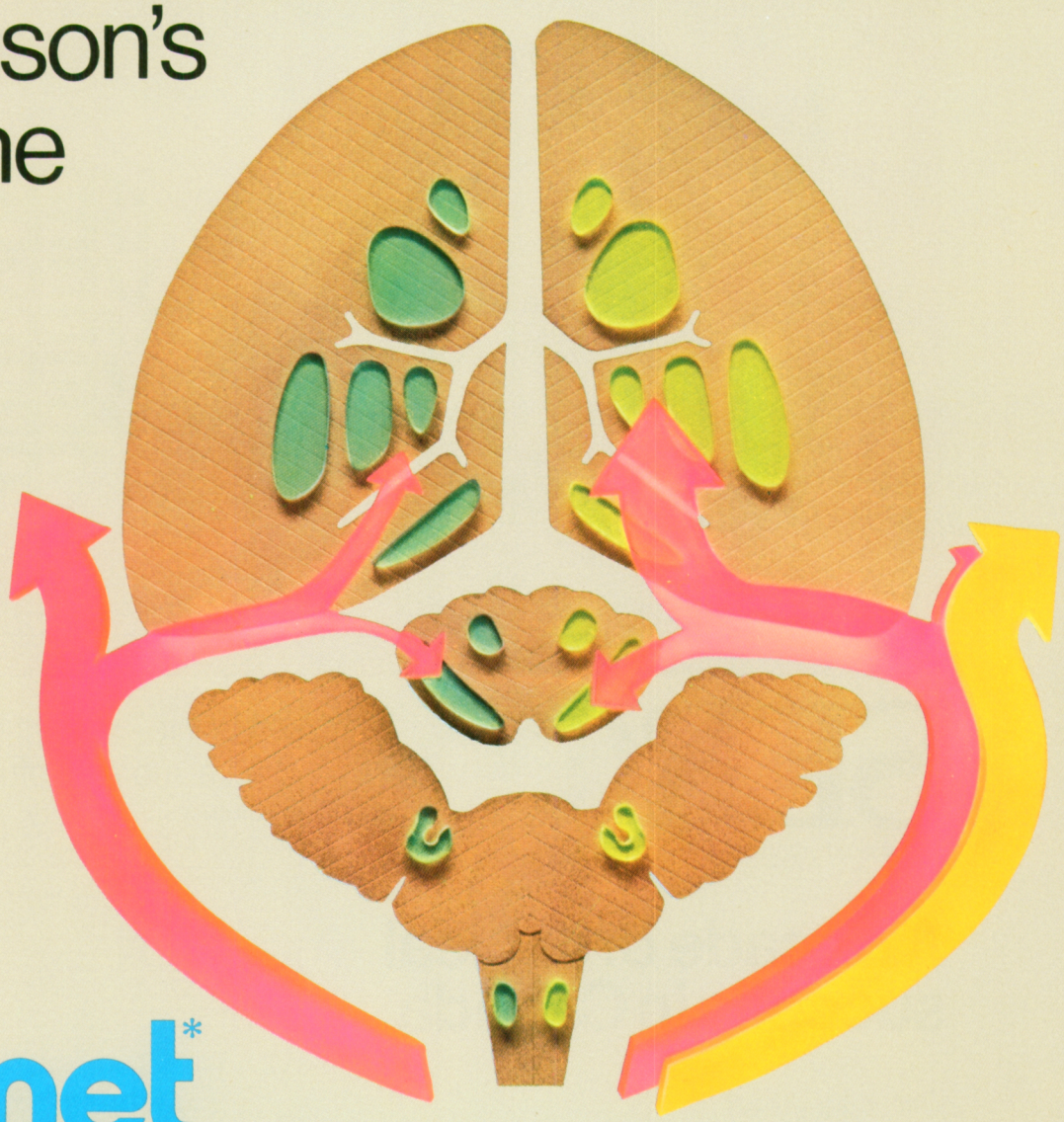
sinemet*

(levodopa and carbidopa combination)

the emerging standard of therapy in Parkinson's syndrome



sinemet*

by efficiently increasing the cerebral supply of dopamine

- ☐ permits control of the major symptoms particularly rigidity and bradykinesia
- ☐ enables patients to lead more normal lives

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.

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sinemet*

(levodopa and carbidopa combination)

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, nonspecific 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 dyskinesias.
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
Ca 8804—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.

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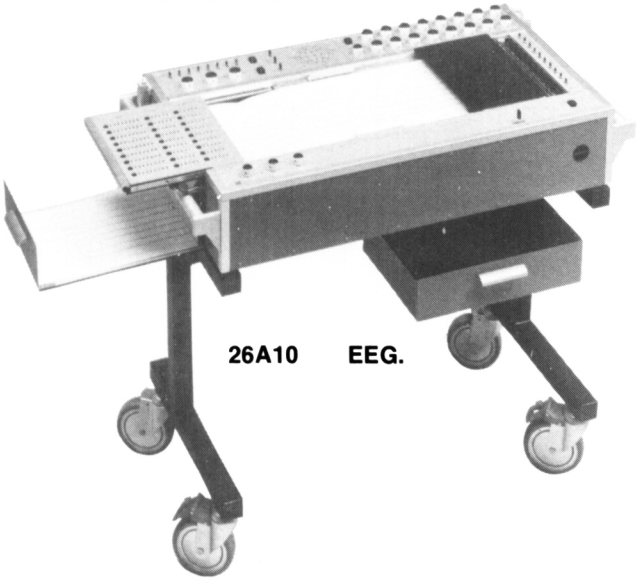
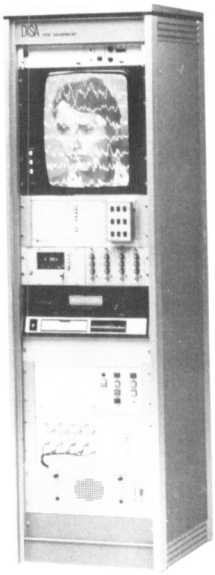


26A10 EEG.



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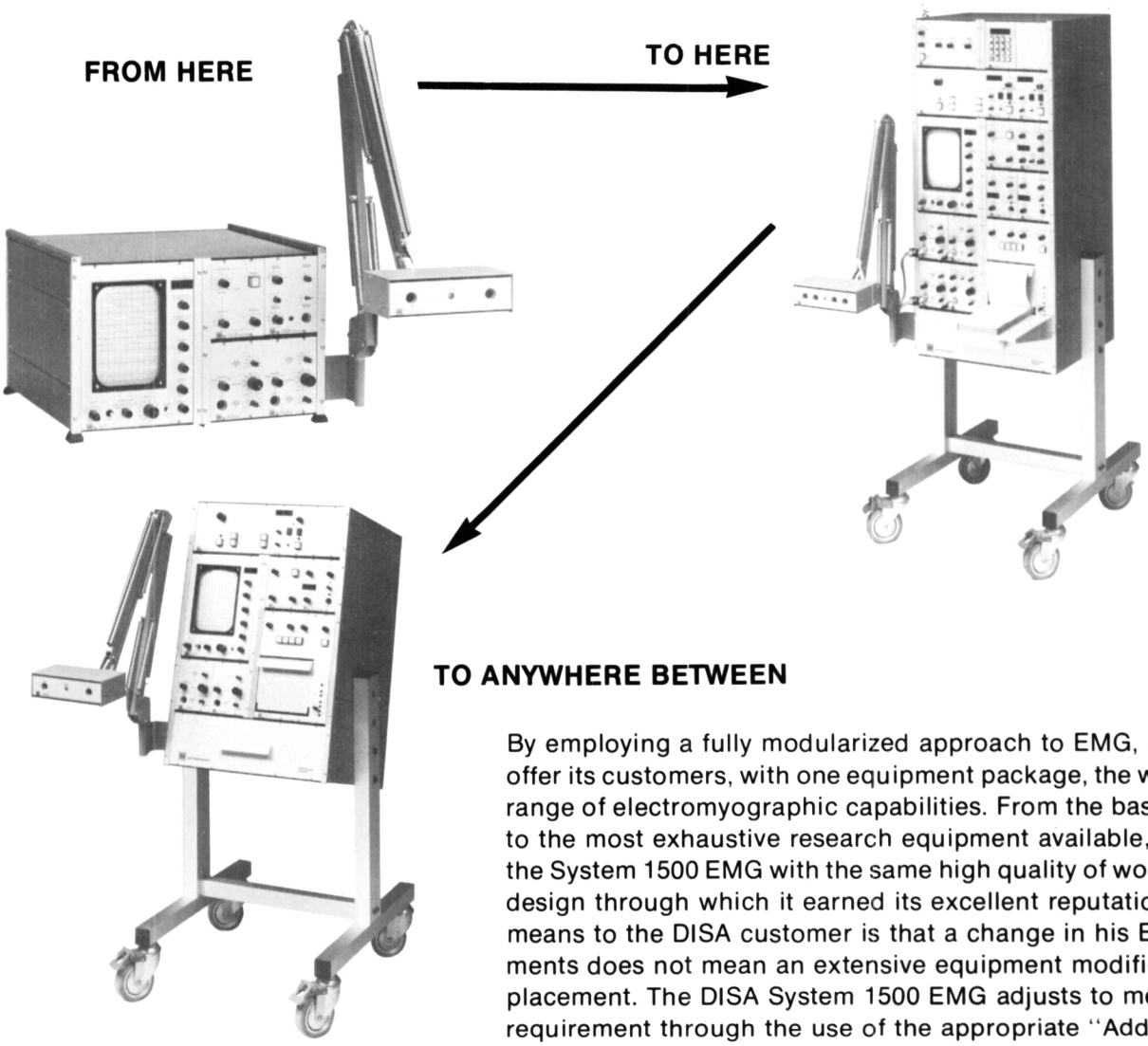
1500 DIGITAL EMG SYSTEMS



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