

THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES

LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES

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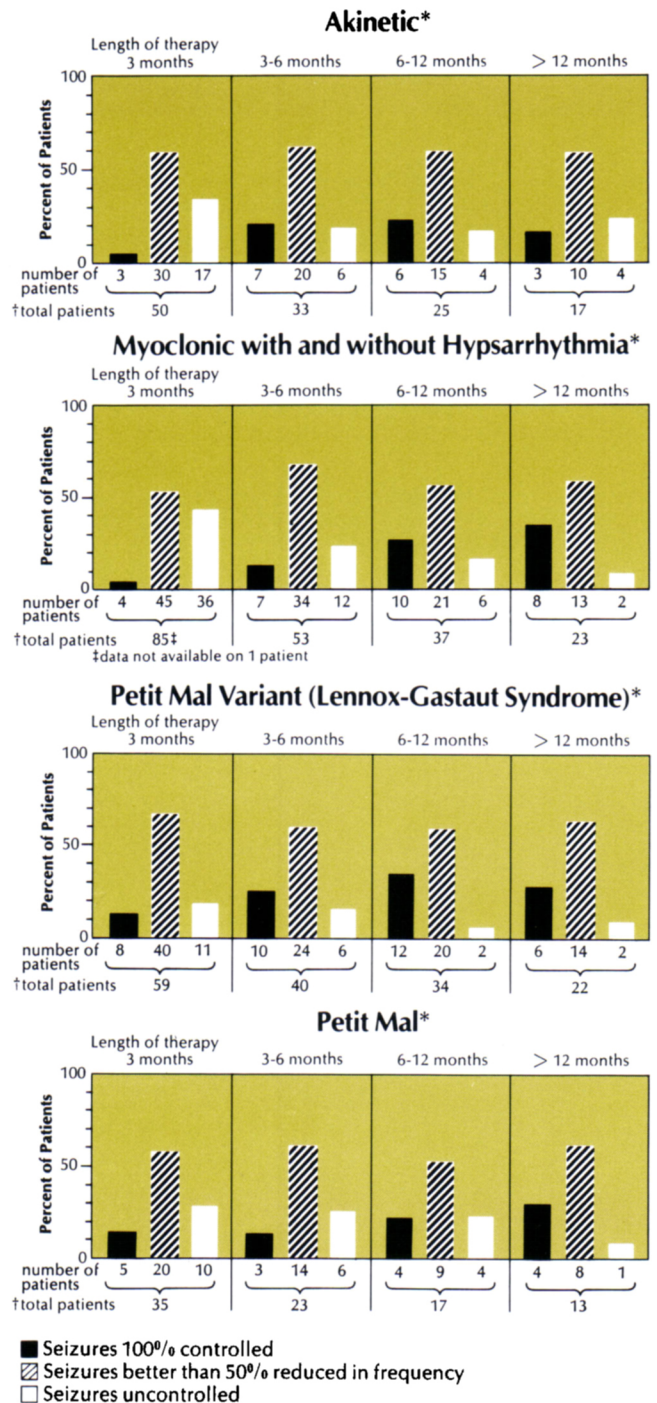
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- it may be of value as principal medication in petit mal where succinimide therapy has failed.
- the most frequently noted side effects, drowsiness and ataxia, generally are dose related and can often be controlled by dosage adjustments.

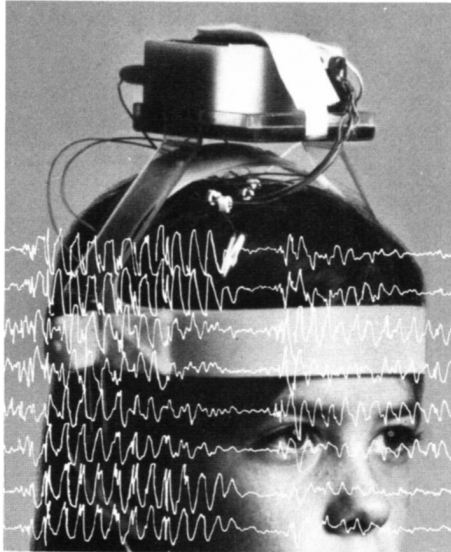
Effect of RIVOTRIL on seizure frequency



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† 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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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.

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often a more helpful approach

REFERENCES

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10. Hommes, O. R.: A study of the efficacy of betahistine in Meniere's syndrome. *Acta oto-laryng. Supplement* 305:70, 1972.

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.

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

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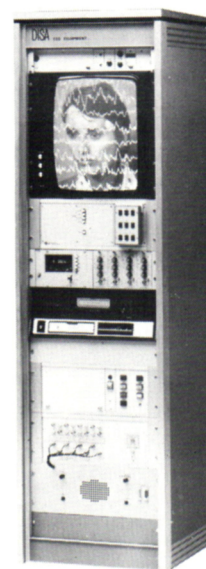
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Tegretol[®]

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 sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus erythematosus.

Neurological reactions:

The reactions reported as occurring during treatment with Tegretol include vertigo, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements and increase in motor seizures. In addition, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, and tinnitus have been reported but only very rarely. There have been some reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of Tegretol could be established.

Cardiovascular systems:

Recurrence of thrombophlebitis in patients with a prior history of thrombophlebitis, congestive heart failure, aggravation of hypertension, 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 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 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  signet.

Availability

Bottles of 50 and 500 tablets. Protect from moisture.

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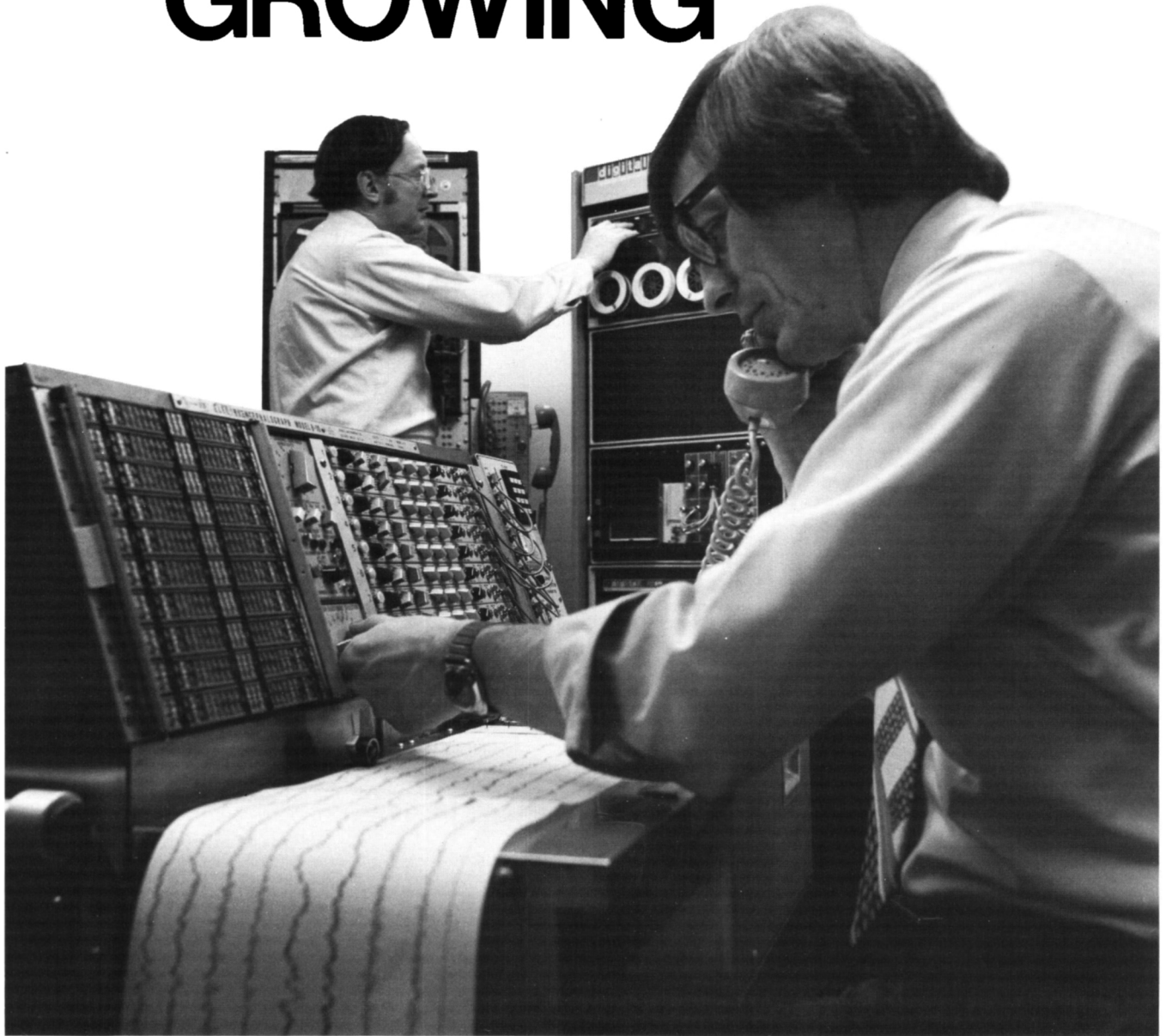
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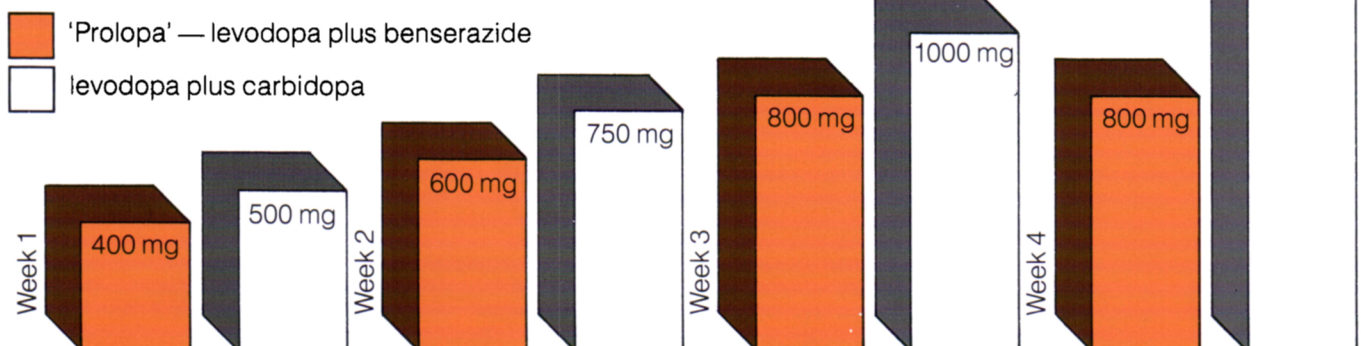
Progress for the Parkinsonian Patient

Prolopa®



- 1971** Roche was the first to introduce levodopa (Larodopa*), a drug which could substantially improve the life of the Parkinsonian patient.
- 1977** Continuous research and clinical trials enables Roche to introduce 'Prolopa' (levodopa plus the decarboxylase inhibitor benserazide in a 4:1 ratio). 'Prolopa' provides significant advantages for the patient and physician:
- An equal degree of improvement to that obtained with levodopa alone in the signs and symptoms of Parkinson's disease.¹
 - A marked reduction (approximately fivefold) in the daily dosage of levodopa needed to obtain a satisfactory response from patients.^{2,3}
 - A more rapid clinical response. Maximum benefit achieved in days as opposed to months with levodopa.⁴
 - Less frequent occurrences of the side effects of nausea and vomiting with 'Prolopa' than with levodopa only.⁵
 - A simpler dosage regimen.²
 - Within the range of recommended doses, less levodopa is required to reach optimal dosage for most patients than with the combination of L-dopa plus carbidopa.⁶

Levodopa daily intake based on the maximum recommended doses for a patient not receiving levodopa. (Calculated from Manufacturers' Product Monographs.)



'Prolopa': Initially, one capsule b.i.d., increasing by one capsule every three days to a maximum of eight capsules. Combination of levodopa plus carbidopa: Initially ½ tablet b.i.d., increasing by ½ tablet every three days to a maximum of five tablets.

Brief Prescribing Information

Classification

Antiparkinsonism agent

Indications

The treatment of Parkinson's syndrome with the exception of drug-induced parkinsonism.

Contraindications

Patients with a known sensitivity to levodopa or benserazide. In patients in whom sympathomimetic amines are contraindicated; in conjunction with monoamine oxidase inhibitors or within two weeks of their withdrawal. Clinical or laboratory evidence of uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; in narrow angle glaucoma (may be used in wide-angle glaucoma provided that the intra-ocular pressure remains under control). History of melanoma or with suspicious undiagnosed skin lesions.

Warnings

Discontinue levodopa therapy at least twelve hours before initiation of 'Prolopa' therapy. To avoid inducing central nervous system side effects (abnormal movements) dosage of 'Prolopa' 100-25 should be increased gradually. Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Exercise caution in patients with a history of psychotic disorders or who are receiving psychotherapeutic agents such as reserpine, pheno-thiazines or tricyclic anti-depressants.

Administer with care to patients with a history of myocardial infarction or who have atrial, nodal or ventricular arrhythmias. The safety of 'Prolopa' in patients under 18 years has not been established. In women of childbearing potential who are or who may become pregnant the anticipated benefits of the drug should be weighed against the possible hazards to mother and fetus. 'Prolopa' should not be given to nursing mothers.

Precautions

Patients with a history of convulsive disorders should be treated cautiously with 'Prolopa'. Upper gastrointestinal hemorrhage may occur in patient with a history of peptic ulcer.

Patients who improve on 'Prolopa' therapy should be advised to resume normal activities gradually as rapid mobilization may increase the risk of injury. 'Prolopa' should be administered with caution to patients on antihypertensive medication.

Adverse Reactions

Abnormal involuntary movements are the most common adverse reactions with 'Prolopa'. These are usually dose-dependent and may disappear or become tolerable after dose reduction. Periodic oscillations in performance, end-of-dose akinesia, on-off phenomenon and akinesia paradoxa constitute the most serious problems encountered after prolonged 'Prolopa' therapy. Side effects such as nausea and vomiting, which are frequently observed during the initial stages of levodopa therapy, are much less common in patients treated with 'Prolopa'. Cardiovascular disturbances such as arrhythmias and orthostatic hypotension are less frequent than in patients treated with levodopa alone. Psychiatric disturbances including mild elation, depression, anxiety, agitation, aggression, hallucinations and delusions are also encountered.

Dosage

Recommended initial dose is one capsule of 'Prolopa' 100-25 once or twice a day. This dose may be carefully increased by one capsule every third or fourth day until an optimal therapeutic effect is obtained without dyskinesias. Near the upper limits of dosage, the increments should be made slowly, at 2-4 week intervals.

Optimal dosage for most patients is 4-8 capsules of 'Prolopa' 100-25 daily (400-800 mg levodopa), divided into 4-6 doses. Most patients require no more than 6 capsules of 'Prolopa' 100-25 (600 mg levodopa), per day.

'Prolopa' 200-50 capsules are intended only for maintenance therapy once the optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patient should receive more than 5-6 capsules of 'Prolopa' 200-50 daily (1000-1250 mg levodopa in combined therapy), during the first year of treatment.

Supply

'Prolopa' 100-25 capsules containing 100 mg levodopa and 25 mg benserazide and 'Prolopa' 200-50 capsules containing 200 mg levodopa and 50 mg benserazide, in bottles of 100.

References

1. Fazio, C. et al.: Treatment of Parkinson's Disease with L-dopa and Association L-dopa plus a DOPA Decarboxylase Inhibitor. *Z. Neuro.*, 202:347. (1972).
2. Barbeau, A.: Treatment of Parkinson's Disease with L-dopa and Ro 4-4602: Review and Present Status. *Advance in Neurology*, Ed.: D.B. Clane, Raven Press, New York, 2:173. (1973).
3. Rinne, U.K. et al.: Treatment of Parkinson's Disease with L-dopa and Decarboxylase Inhibitor. *Neuro.*, 202:1. (1972).
4. Schneider, E. et al.: Wirkungsvergleich von L-dopa und der Kombination L-dopa Decarboxylasehemmer beim Parkinson-Syndrom. *Arch. Psychiat. Nervenkr.*, 217:95. (1973).
5. Steinhausl, H.: Erfahrungsbericht über die Behandlung des Parkinson-Syndroms mit dem Kombinationspräparat L-dopa Dekarboxylasehemmer (Ro-8-0576). *Wien. med. Wschr.*, 123:433. (1973).
6. Manufacturers' Product Monographs.


Prolopa[®]

a choice after comparisons

Product monograph available upon request

*Registered Trade Mark for levodopa plus benserazide

*Registered Trade Mark for levodopa

 Hoffmann-La Roche Limited
Vaudreuil, Québec



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.

^{*}Trademark

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 child-bearing 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 Anti-hypertensive Therapy:** Asymptomatic 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 akinesic crises related to dyskinesias, akinesia paradoxa (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, akinesic episodes, "akinesia paradoxa", increase in the frequency and duration of the oscillations in performance, torticollis, trismus, tightness of the mouth, lips or tongue, oculogyric crisis, weakness, numbness, bruxism, priapism. **Gastrointestinal:** constipation, diarrhea, epigastric and abdominal distress and pain, flatulence; eructation, hiccups, sialorrhea; difficulty in swallowing, bitter taste, dry mouth; duodenal ulcer; gastrointestinal bleeding; burning sensation of the tongue. **Cardiovascular:** arrhythmias, hypotension, non-specific ECG changes, flushing, phlebitis. **Hematologic:** hemolytic anemia, leukopenia, agranulocytosis. **Dermatologic:** sweating, edema, hair loss, pallor, rash, bad odor, dark sweat. **Musculoskeletal:** low back pain, muscle spasm and twitching, musculoskeletal pain. **Respiratory:** feeling of pressure in the chest, cough, hoarseness, bizarre breathing pattern, postnasal drip. **Urogenital:** urinary frequency, retention, incontinence, hematuria, dark urine, nocturia, and one report of interstitial nephritis. **Special Senses:** blurred vision, diplopia, dilated pupils, activation of latent Horner's syndrome. **Miscellaneous:** hot flashes, weight gain or loss. Abnormalities in laboratory tests reported with levodopa alone, which may occur with SINEMET*: Elevations of blood urea nitrogen, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase or protein bound iodine. Occasional reduction in WBC, hemoglobin and hematocrit. Elevations of uric acid with colorimetric method. Positive Coombs tests reported both with SINEMET* and with levodopa alone, but hemolytic anemia extremely rare.

DOSAGE SUMMARY

In order to reduce the incidence of adverse reactions and achieve maximal benefit, therapy with SINEMET must be individualized and drug administration continuously matched to the needs and tolerance of the patient. Combined therapy with SINEMET* has a narrower therapeutic range than with levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and recommended dosage ranges not be exceeded. Appearance of involuntary movements should be regarded as a sign of levodopa toxicity and an indication of overdose, 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.

*Trademark

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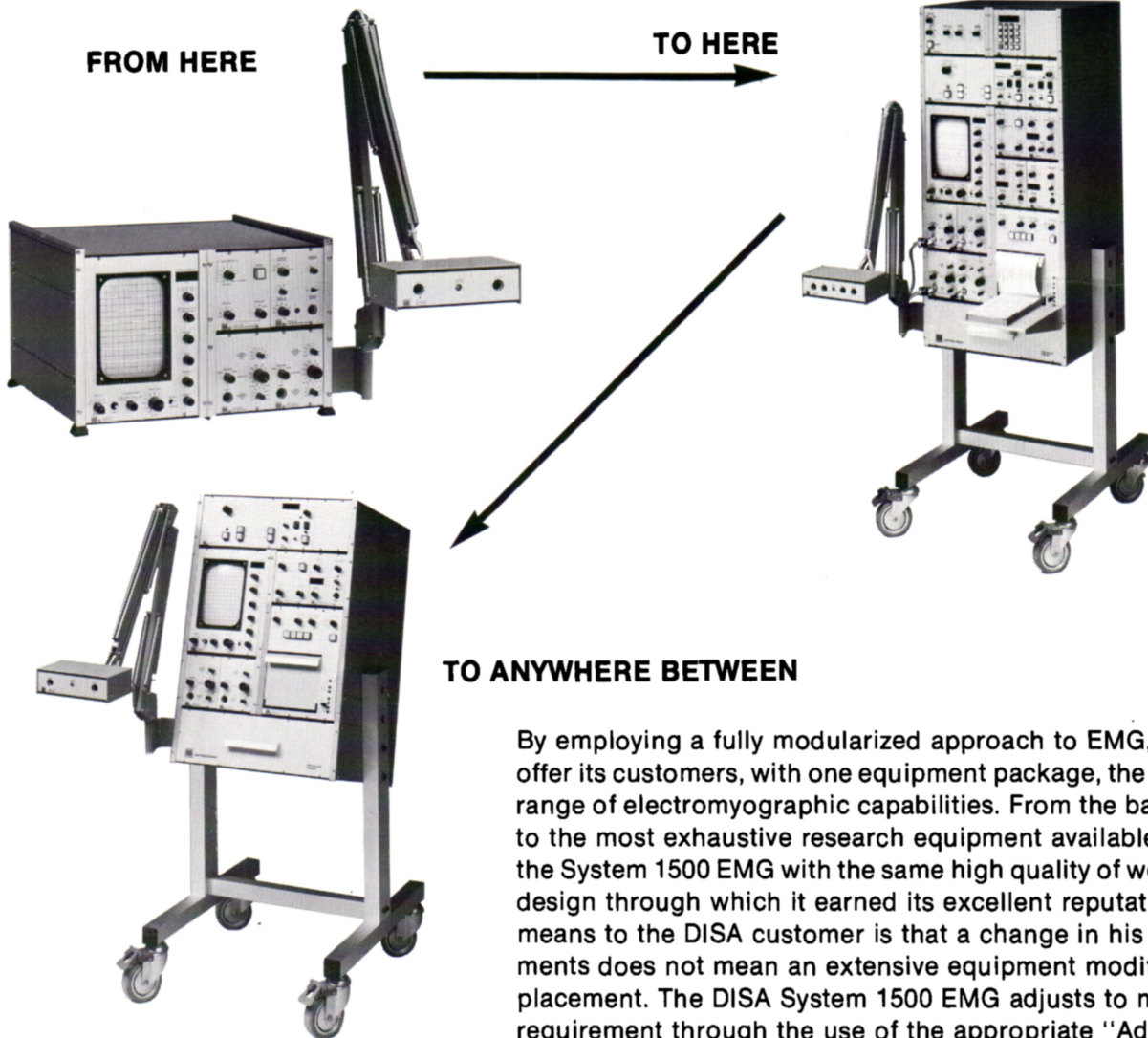
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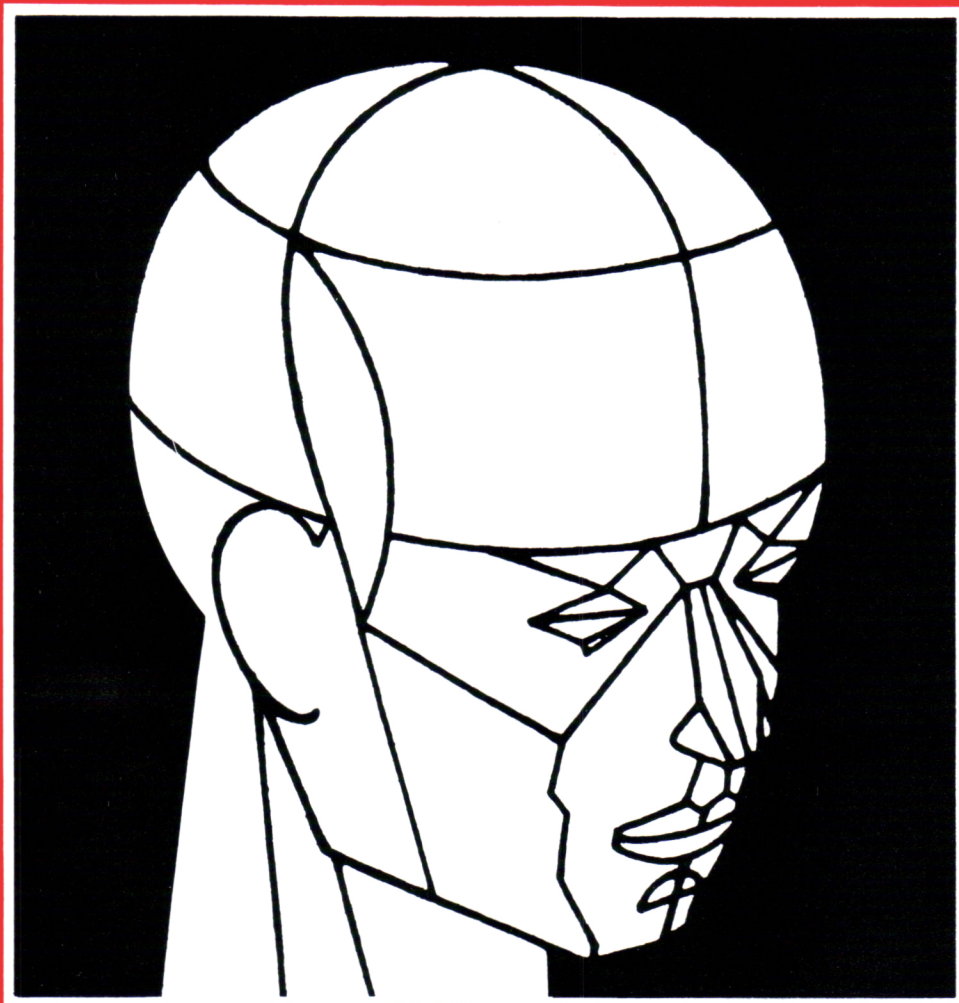
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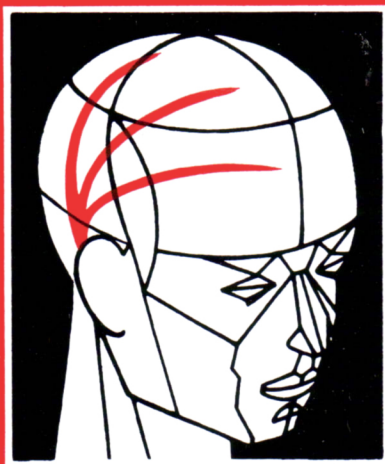
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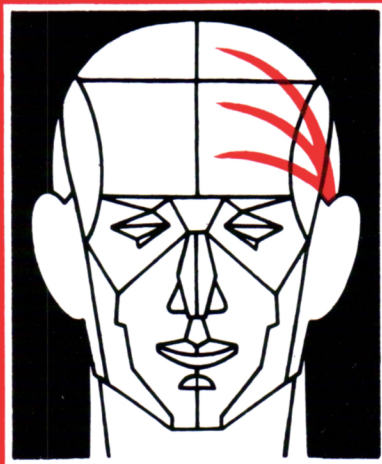
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Full product information is available upon request.

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