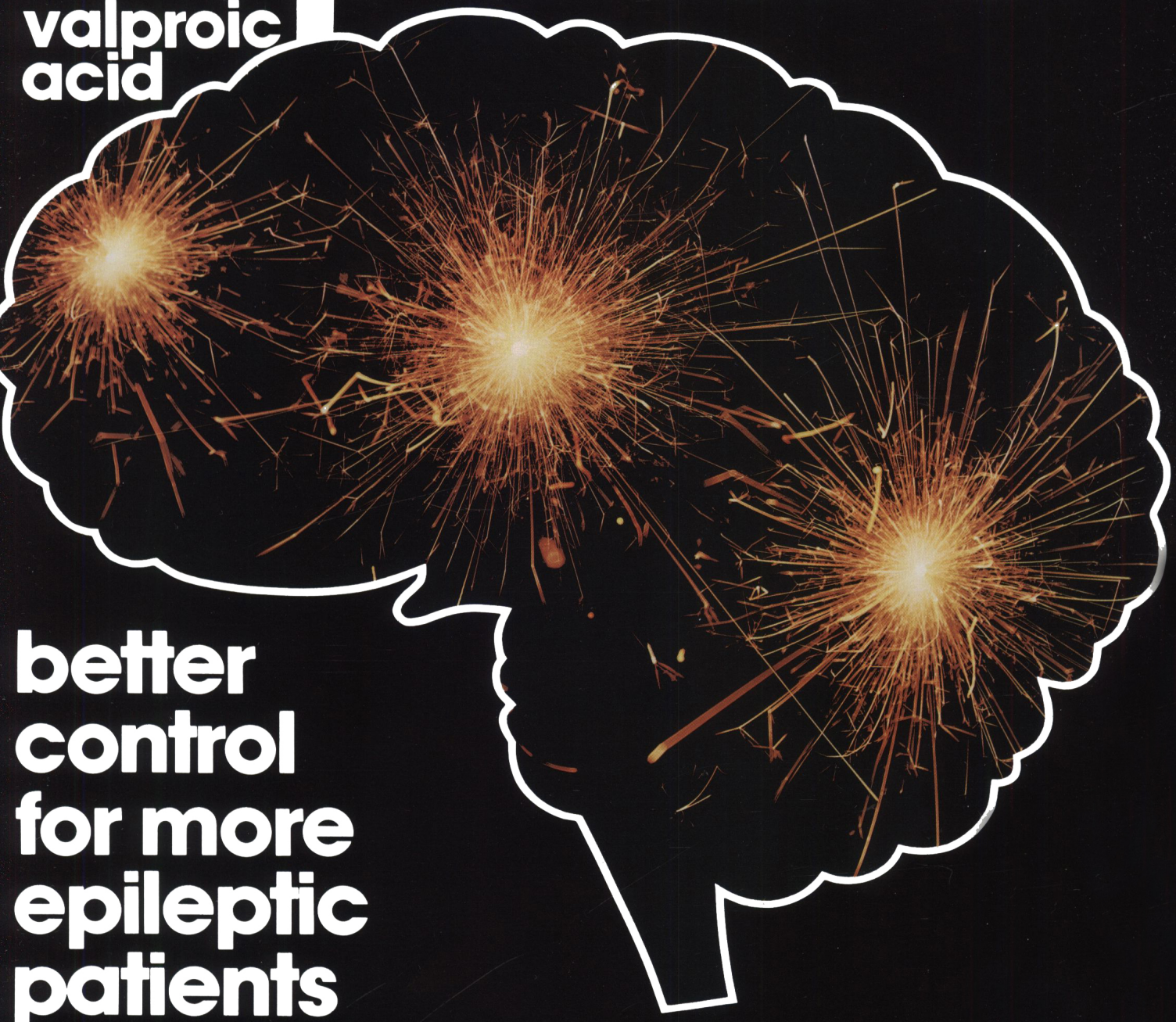
Depakene*

valproic acid



better control for more epileptic patients

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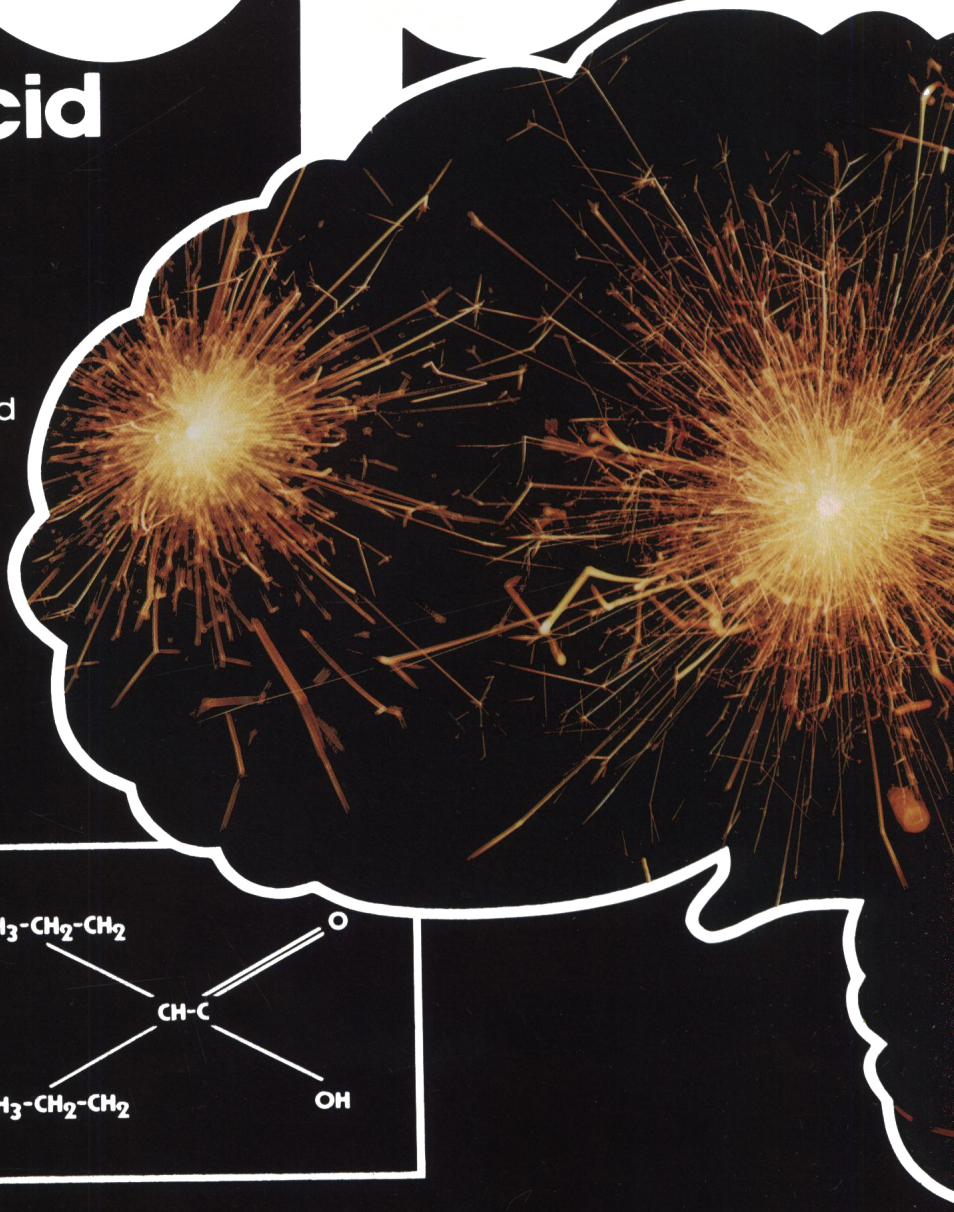
Depa

valproic acid



A major advance in anti-convulsant therapy that could bring more epileptic patients closer to normal.
as sole and adjunctive treatment of simple or complex absence seizures, including petit mal.
as adjunctive therapy of multiple seizures that include absence attacks.

a unique chemical structure

DEPAKENE is a simple fatty acid, chemically unrelated to other anticonvulsants.

a physiological mode of action

DEPAKENE appears to increase GABA (γ-aminobutyric acid) levels in the brain and cerebellum. GABA is known to inhibit neuronal excitability.[1]

Depakene extends the range

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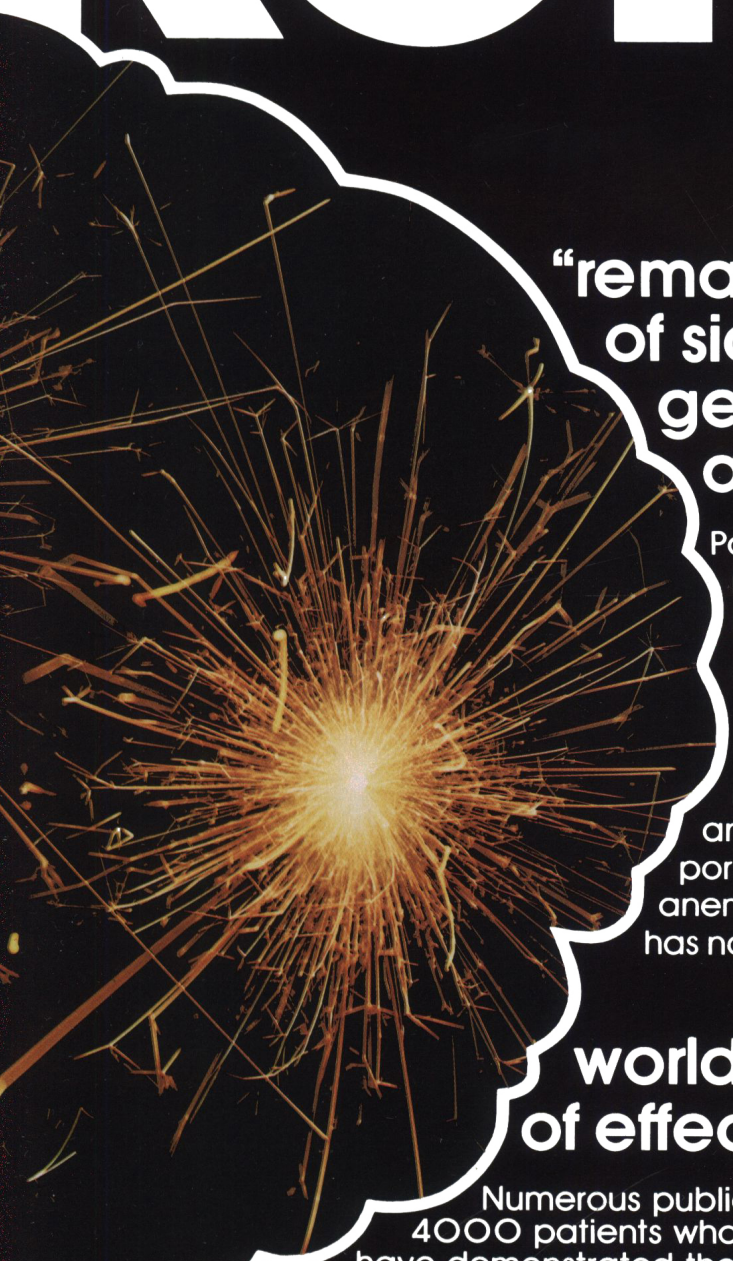
kene



"remarkably free of side effects in the general context of antiepileptics"[3]

Patients taking DEPAKENE have been reported to be more lively and alert and better able to carry out their daily tasks.[3]

DEPAKENE has not been associated with cosmetically undesirable side effects such as hirsutism, acne and gum hyperplasia. Although inhibition of platelet aggregation and leukopenia have been occasionally reported, it has not been associated with aplastic anemia or agranulocytosis. And DEPAKENE has no record of tolerance in long-term use.[2]

world-wide documentation of effectiveness

Numerous publications and clinical trials involving more than 4000 patients whose ages ranged from 5 months to 71 years, have demonstrated the antiepileptic efficacy of DEPAKENE.

An overview of clinical studies[2] involving valproic acid in 1020 patients demonstrates an excellent (75-100%) reduction in seizure frequency in 45.7% of patients, and satisfactory results (33-74% reduction of seizures) in 25.4% more.

of anticonvulsant therapy.

Depakene
valproic acid

Prescribing Information

CLINICAL PHARMACOLOGY

Depakene (valproic acid) has anticonvulsant properties. Although its mechanism of action has not yet been established, it has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

Valproic acid is rapidly absorbed after oral administration. Peak serum levels occur approximately one to four hours after a single oral dose. The serum half-life ($t_{0.5}$) of valproic acid is approximately 8 to 12 hours. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. The therapeutic plasma concentration range is believed to be from 43 to 86 μg/mL.

Excretion of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The principal metabolite formed in the liver is the glucuronide conjugate.

INDICATIONS AND CLINICAL USE

Depakene (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple seizure types which include absence.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS

Depakene (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in a few patients receiving Depakene (valproic acid) and concomitant anticonvulsant drugs. These events have occurred during the first six months of treatment with valproic acid. Although a causal relationship has not been established, caution should be observed when administering Depakene to patients with pre-existing liver disease. Liver function tests should be performed prior to therapy and every two months thereafter.

Use in pregnancy

The safety of Depakene (valproic acid) during pregnancy has not been established, however, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks in treating or counselling women of childbearing age who have epilepsy.

Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased two to threefold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

Nursing Mothers

Depakene is secreted in breast milk. As a general rule, nursing should not be undertaken while a patient is receiving Depakene.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 350 mg/kg/day in rats and 90 mg/kg/day in dogs. The effect of Depakene (valproic acid) on the development of the testis and on sperm production and fertility in humans is unknown.

PRECAUTIONS

General

Because of rare reports of platelet aggregation dysfunction, thrombocytopenia and elevated liver enzymes, it is recommended that liver function tests, platelet counts and bleeding time determinations be performed before initiation of therapy and at periodic intervals.

Because valproic acid may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see Drug Interactions).

Valproic acid is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

Driving and Hazardous Occupations

Valproic acid may produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions

Depakene (valproic acid) may potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, although the mechanism is unknown. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin. It is not known if there is a change in unbound (free) phenytoin serum levels. The dose of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

Caution is recommended when valproic acid is administered with drugs affecting coagulation, e.g. acetylsalicylic acid and warfarin (see Adverse Reactions).

ADVERSE REACTIONS

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since Depakene (valproic acid) has usually been used with other anticonvulsants, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal

Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects

Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes," tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients who were also on phenobarbital.

Dermatologic

Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal

Weakness has been reported.

Hematopoietic

Valproic acid inhibits the secondary phase of platelet aggregation. This may be reflected in altered bleeding time. Relative lymphocytosis and mild thrombocytopenia have also been noted in isolated cases. Leukopenia has been reported.

Hepatic

Increases in serum alkaline phosphatase and serum glutamic oxaloacetic transaminase have been noted. Isolated cases of severe hepatotoxicity have been reported (see Warnings).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In a reported case of overdosage with Depakene (valproic acid) after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION

Depakene (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dose is 30 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen.

Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Number of Capsules or Teaspoonsful of Syrup		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	0	0	1
25-39.9	55-87.9	500	1	0	1
40-59.9	88-131.9	750	1	1	1
60-74.9	132-164.9	1,000	1	1	2
75-89.9	165-197.9	1,250	2	1	2

As the dosage of valproic acid is raised, blood levels of phenobarbital and/or phenytoin may be affected (see Precautions).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. The capsules should be swallowed without chewing to avoid local irritation of the mouth and throat.

AVAILABILITY

Depakene (valproic acid) is available as orange-coloured, soft-gelatin capsules of 250 mg in bottles of 100 and as a red syrup containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL in bottles of 450 mL. Depakene is a prescription drug (Schedule F).

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PHARMACEUTICAL PRODUCTS DIVISION
ABBOTT LABORATORIES, LIMITED
MONTREAL, CANADA, H4P 1A5

Full product monograph on request.

T.M.

PAAB

MEMBER PMAC

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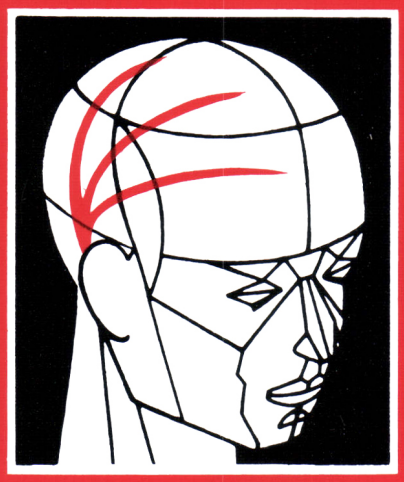
Vascular headaches
of the migraine type

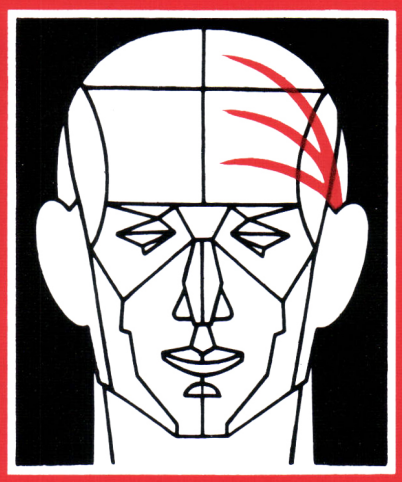
℞ **CAFERGOT®** tablets
℞ **GYNERGEN®** tablets and injections

Symptomatic treatment of classic, common, or cluster migraine.



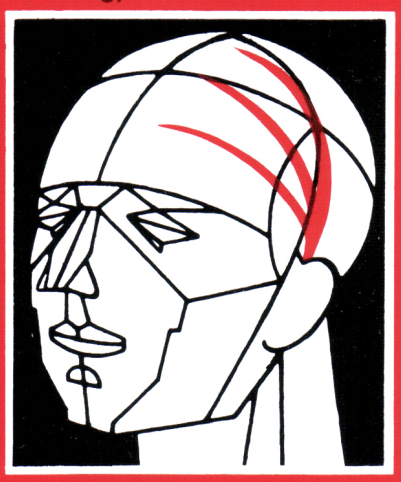
℞ **SANDOMIGRAN®** tablets
℞ **SANSERT®** tablets

Prophylactic treatment of frequent, recurring vascular headaches.



℗ **CAFERGOT®-PB** tablets and suppositories

Symptomatic treatment of classic, common, or cluster migraine (accompanied by nervous tension, nausea and vomiting).



Tension headaches
(muscle contraction)

℗ **FIORINAL®** tablets and capsules
Ⓝ **FIORINAL®-C ¼** capsules
Ⓝ **FIORINAL®-C ½** capsules

Symptomatic treatment of muscle contraction headache (tension headache).

Other non-vascular headaches

℗ **FIORINAL®** tablets and capsules
Ⓝ **FIORINAL®-C ¼** capsules
Ⓝ **FIORINAL®-C ½** capsules

Symptomatic treatment of other non-vascular headaches (headaches associated with dysmenorrhea, sinusitis, febrile diseases, cold and grippe, overeating, hangover).

Full product information is available upon request.

Contact your Sandoz representative or write to the Medical Services Department of Sandoz (Canada) Limited for a complimentary supply of our new diagnostic aid - the patient's "HEADACHE HISTORY" or for information about our audio visuals concerning the diagnosis and treatment of headaches.

SANDOZ®

SANDOZ (CANADA) LIMITED
P.O. BOX 385, DORVAL, QUEBEC H9R 4P5

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Progress for the Parkinsonian Patient

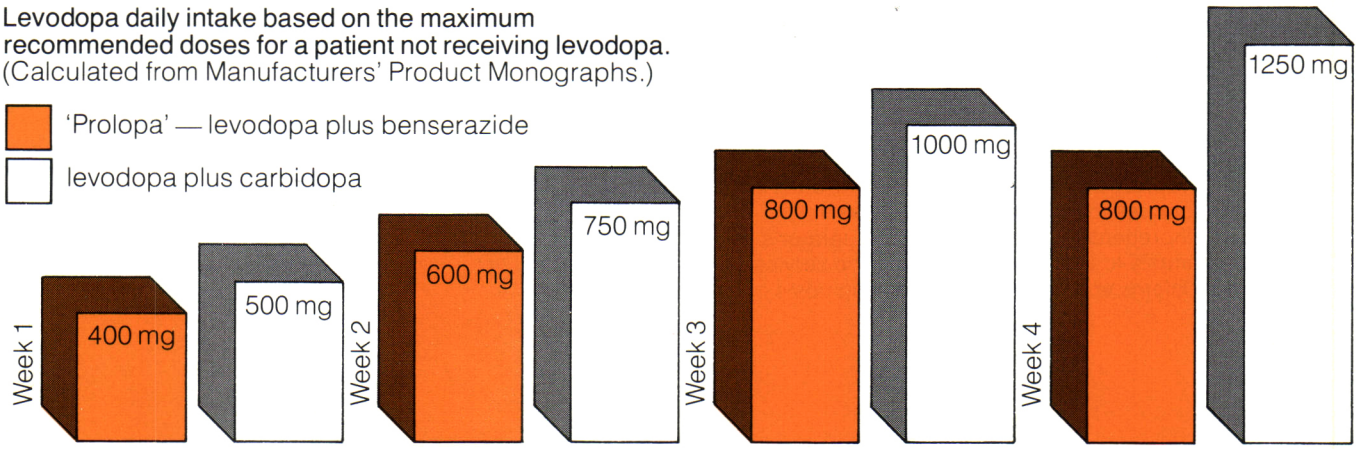
Prolopa®

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.

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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 tricycle 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 paradoxica 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

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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

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Results of a Recent Post-Myocardial

ANTURAN REDUCED
(sulfinpyrazone)
ANNUAL CARDIAC DEATH RATE BY 48.5%
COMPARED WITH PLACEBO.

The Trial

A prospective, randomized, double-blind, multi-center study analyzing 1,475 patients, comparing the effect of Anturan 200 mg q.i.d. and placebo in the prevention of cardiac mortality in patients with recent myocardial infarction.

Twenty-one U.S. and five Canadian hospitals participated in the trial.

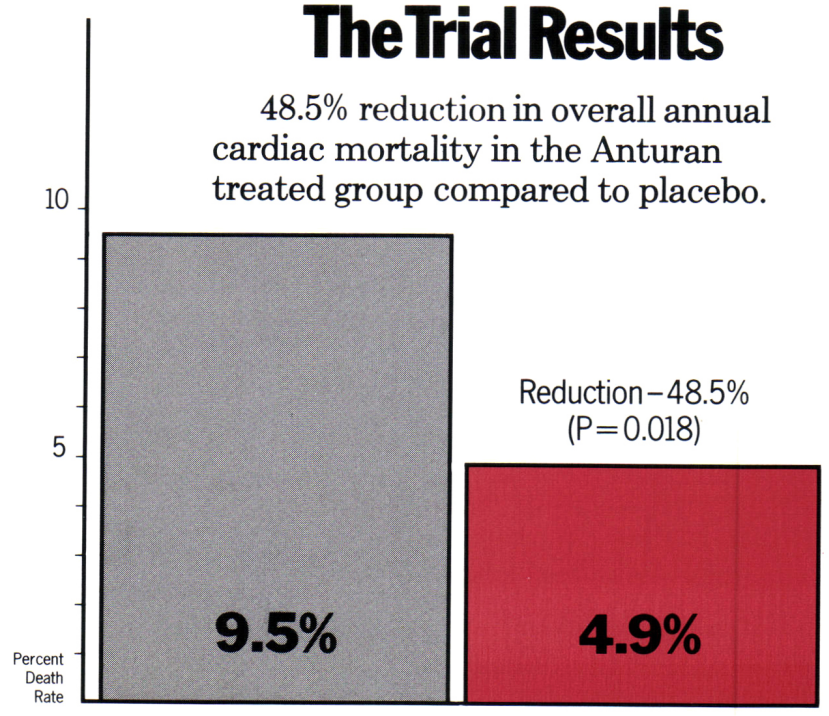
The co-ordinators consisted of representatives of the medical, epidemiological and biostatistical communities of Canada and the U.S.

REFERENCE:
1. Sulfinpyrazone in the Prevention of Cardiac Death after Myocardial Infarction. The Anturan Reinfarction Trial. The Anturan Reinfarction Trial Research Group. In: New England Journal of Medicine, Vol. 298, No. 6, Feb. 9, 1978.

For brief prescribing information, see page 00.

The Trial Results

48.5% reduction in overall annual cardiac mortality in the Anturan treated group compared to placebo.



Death from Cardiac causes

G-8062

https://doi.org/10.1017/S0317167100024100 Published online by Cambridge University Press

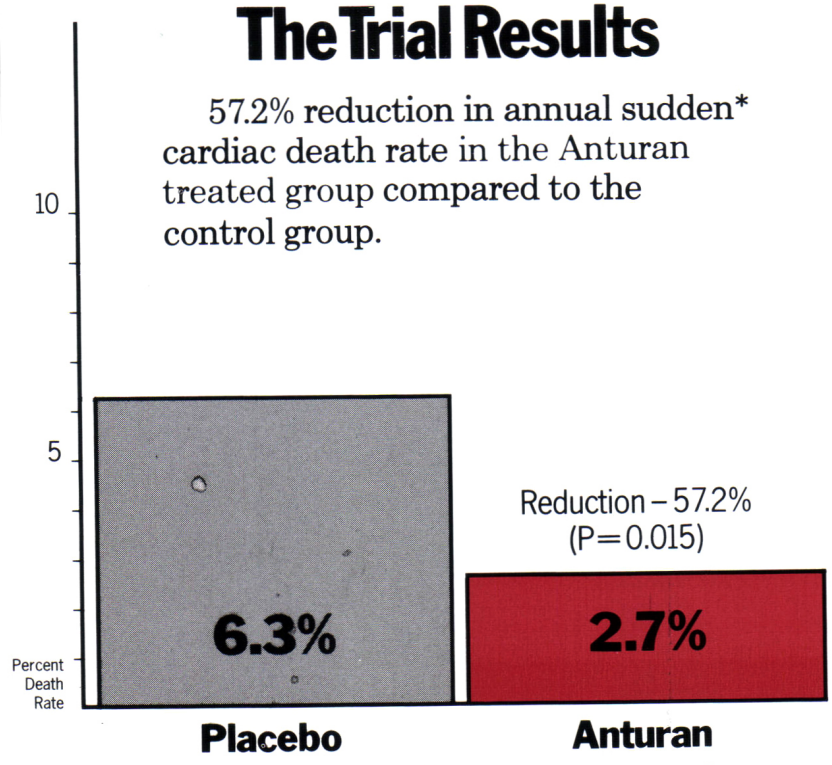
Infarction Trial:[1]

ANNUAL SUDDEN* CARDIAC DEATH RATE BY 57.2%

COMPARED WITH PLACEBO.

The Trial Results

57.2% reduction in annual sudden* cardiac death rate in the Anturan treated group compared to the control group.



"Sudden" Cardiac Death

"The data reflect excellent randomization, compliance with therapy and tolerance of the drug."[1]

Conclusion

"There are approximately 900 deaths per week in the United States among patients who have recently recovered from an acute myocardial infarction. If the benefit of sulfinpyrazone therapy can be shown to be sustained in the later periods of this trial, conservative interpretation of the overall results to date suggest the feasibility of reducing cardiac deaths during the first year after myocardial infarction by 200 to 300 per week."[1]

*Sudden death – within 60 minutes of onset of symptoms.

It's a matter of life.

ANTURAN®
200 mg four times a day

Geigy
Dorval, Que. H9S 1B1

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ANTURAN®
200 mg four times a day

INDICATIONS:
1 Clinical states in which abnormal platelet behavior is a causative or associated factor, as demonstrated by:
- thromboembolism associated with vascular and cardiac prostheses
- recurrent venous thrombosis
- arteriovenous shunt thrombosis

2 Chronic phases of gout, both the intercritical or silent stage and the gouty arthritis stage.

DOSAGE AND ADMINISTRATION:
Thromboembolic conditions: – Usual daily dosage is 600 – 800 mg in divided doses. It is recommended not to exceed 1000 mg (20 mg/kg for a 50 kg man) daily.
Gout: – Usual daily dosage is 200 – 400 mg in divided doses. This average dosage may be increased to 800 mg if necessary, or reduced to 200 mg when urate blood level has been satisfactorily controlled. Minimum effective dose should be maintained indefinitely without interruption even during acute attacks, which should be treated concomitantly with either Butazolidin or colchicine.

The change from other uricosuric agents to Anturan should be made at full dosage.

It is important to distribute the total dose as well as possible over a 24-hour period. It is recommended that Anturan be taken with meals.

CONTRAINDICATIONS:
The safe use of sulfinpyrazone in pregnancy has not been established. It should not be used during pregnancy unless in the opinion of the treating physician the expected benefits outweigh the potential risks.

Active peptic ulcer.

Known hypersensitivity to sulfinpyrazone and other pyrazolone derivatives. Severe hepatic or renal disease, unless due to platelet aggregates.

WARNINGS:
Avoid salicylate therapy, unless administered under careful supervision:
(i) Salicylates and citrates antagonize the uricosuric action of sulfinpyrazone and may therefore interfere with uric acid excretion.
(ii) Salicylates may cause unpredictable and at times, serious prolongation of the bleeding time and in combination with sulfinpyrazone may cause bleeding episodes. If during Anturan therapy, aspirin or another chemically-related drug must be used, patients should be urged to report immediately any undue bleeding episode.

It should be administered with care to patients with a history of healed peptic ulcer.

PRECAUTIONS:
As with all pyrazole compounds, patients receiving Anturan should be kept under close medical supervision and periodic blood counts are recommended.

Recent reports have indicated that Anturan potentiates the action of sulfonamides, e.g., sulfadiazine, sulfisoxazole. Other pyrazole compounds e.g., phenylbutazone, potentiate the hypoglycemic effects of sulfonylureas. There have also been reports that phenylbutazone enhances the effects of insulin in diabetics. Therefore, it is recommended that Anturan be used with caution in conjunction with insulin, sulfonamides, the sulfonylurea hypoglycemic agents and, in general, with agents known to displace, or to be displaced by, other substances, such as penicillin, from serum albumin binding sites.

Because Anturan is a potent uricosuric agent, it may precipitate urolithiasis and renal colic, especially in the initial stages of therapy, in hyperuricemic patients. For this reason, an adequate fluid intake and alkalinization of the urine are recommended. In cases with significant renal impairment, periodic assessment of renal function is indicated.

Since Anturan modifies platelet behavior and, therefore, interferes with one of the components of the blood-clotting system, it should be used with care in conjunction with certain vitamin K antagonists which inhibit clotting through a different mechanism. Regular estimations of bleeding time should be performed.

ADVERSE REACTIONS:
The most frequently reported adverse reactions to Anturan have been gastric complaints or disturbances. Anturan may aggravate or reactivate peptic ulcer. Gastrointestinal bleeding has been reported.

Skin rashes have been reported in rare instances. When they occur, Anturan should be withdrawn.

Anemia, leukopenia, agranulocytosis, thrombocytopenia have rarely been associated with the administration of Anturan.

DOSAGE FORMS:
Anturan 100 mg: Each white, single scored tablet, imprinted Geigy and bearing the identification code FK, contains 100 mg sulfinpyrazone Geigy standard. Supplied in bottles of 100 and 1,000.
Anturan 200 mg: Each white, sugar-coated tablet, imprinted Geigy, contains 200 mg sulfinpyrazone Geigy standard. Supplied in bottles of 100 and 500.
Product monograph supplied on request.

Geigy
Dorval, Qué. H9S 1B1

G-8062

INDEX TO ADVERTISEMENTS

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Pr Symmetrel® Capsules 100 mg
(amantadine HCl)

for the management of Parkinson's syndrome

✻ **Chemically distinct**
(Not related to levodopa or anticholinergic antiparkinson drugs.)

✻ **Fast onset of action**
(Usually effective within 1 week in contrast to the slower response from levodopa.)

Effective with levodopa

(Either initiated concurrently or added to levodopa. Additional benefit may result — such as smoothing out of fluctuations in performance which sometimes occur when levodopa is administered alone. When the levodopa dose must be reduced because of side effects, the addition of Symmetrel may result in better control of Parkinson's syndrome than is possible with levodopa alone.)

Effective with other anticholinergic antiparkinson drugs

(When these drugs, e.g. benztropine mesylate, provide only marginal benefits, Symmetrel used concomitantly may provide the same degree of control of Parkinson's syndrome, often with a lower dose of anticholinergic medication, and a possible reduction in anticholinergic side effects.)

Effective alone

(Lessening of Parkinsonian symptomatology usually evident within one week in responsive patients.)

CONTRAINDICATIONS "Symmetrel" is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Patients with a history of epilepsy or other "seizures" should be observed closely for possible untoward central nervous system effects.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving "Symmetrel" (amantadine HCl).

Safety of use in pregnancy has not been established. Therefore, "Symmetrel" should not be used in women with childbearing potential, unless in the opinion of the physician, the expected benefit to the patient outweighs the possible risks to the fetus (see Toxicology-Effects on Reproduction).

Since the drug is secreted in the milk, "Symmetrel" should not be administered to nursing mothers.

PRECAUTIONS The dose of "Symmetrel" may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Since "Symmetrel" is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering "Symmetrel" to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when "Symmetrel" is administered concurrently with central nervous system stimulants.

Patients with Parkinson's syndrome improving on "Symmetrel" should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving "Symmetrel" (amantadine HCl) who note central nervous system effects of blurring of vision should be cautioned against driving or working in situations where alertness is important.

"Symmetrel" (amantadine HCl) should not be discontinued abruptly since a few patients with Parkinson's syndrome experienced a Parkinsonian crisis, i.e., sudden marked clinical deterioration, when this medication was suddenly stopped.

The dose of anticholinergic drugs or of "Symmetrel" should be reduced if atropine-like effects appear when these drugs are used concurrently.

ADVERSE REACTIONS Adverse reactions reported below have occurred in patients while receiving "Symmetrel" (amantadine HCl) alone or in combination with anticholinergic antiparkinson drugs and/or levodopa.

The more important adverse reactions are orthostatic hypotensive episodes, congestive heart failure, depression, psychosis and urinary retention, and rarely confusion, reversible leukopenia and neutropenia, and abnormal liver function test results.

Other adverse reactions of less importance which have been observed are: anorexia, anxiety, ataxia, confusion, hallucinations, constipation, dizziness (lightheadedness), dry mouth, headache, insomnia, livedo reticularis, nausea, peripheral edema, drowsiness, dyspnea, fatigue, hyperkinesia, irritability, nightmares, rash, slurred speech, visual disturbance, vomiting and weakness; and very rarely eczematoid dermatitis and oculogyric episodes.

Some side effects were transient and disappeared even with continued administration of the drug.

DOSAGE AND ADMINISTRATION The initial dose of "Symmetrel" is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily. When "Symmetrel" and levodopa are initiated concurrently, "Symmetrel" should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal dose. When used alone, the usual dose of "Symmetrel" is 100 mg twice a day.

Patients whose responses are not optimal with "Symmetrel" (amantadine HCl) at 200 mg daily may benefit from an increase to 300 mg daily in divided doses. Patients who experience a fall-off of effectiveness may regain benefit by increasing the dose to 300 mg daily; such patients should be supervised closely by their physicians.

DOSAGE FORMS CAPSULES: (bottles of 100) - each red, soft gelatin capsule contains 100 mg of amantadine HCl.

Product monograph, with complete references, available upon request.

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