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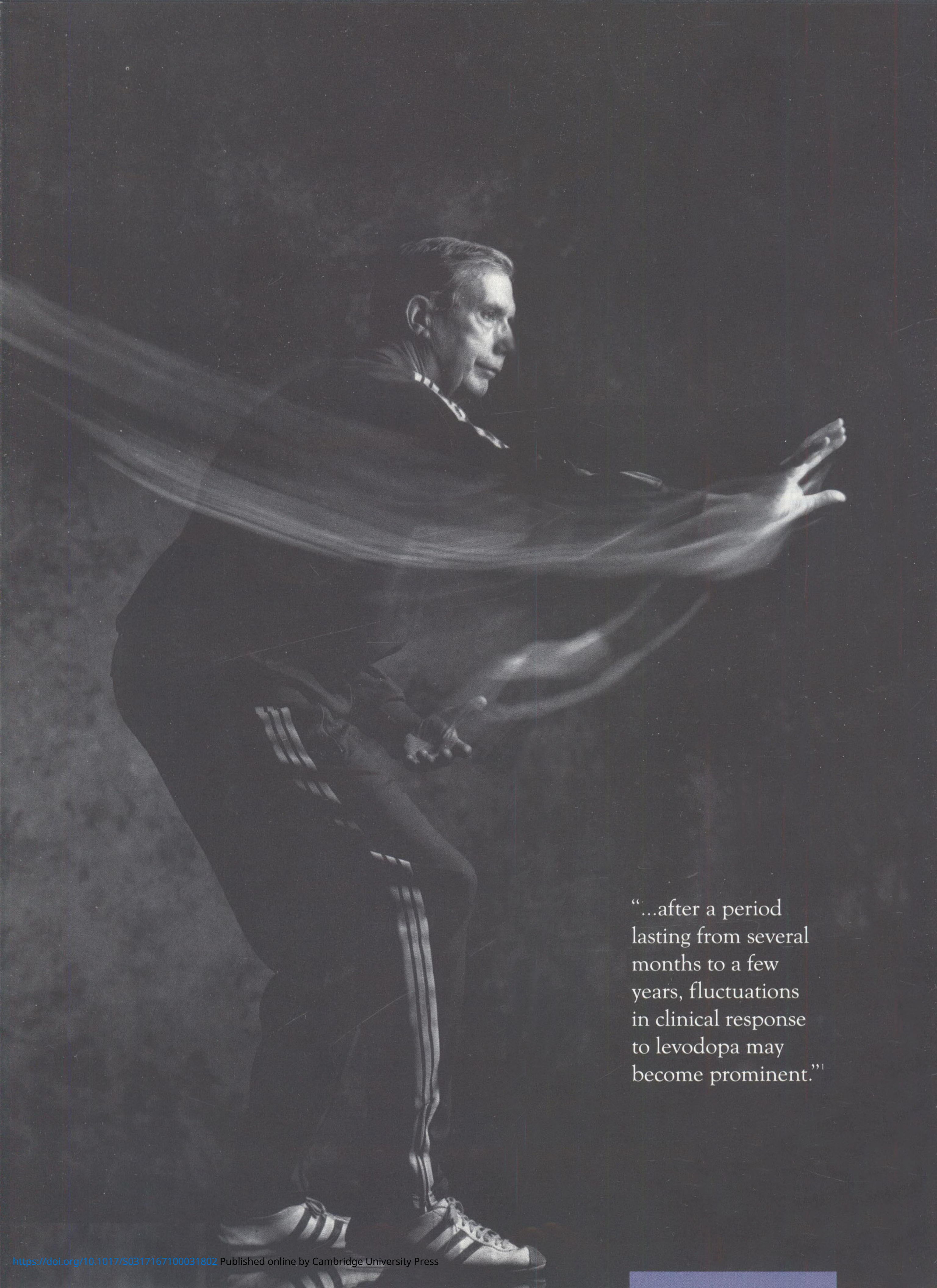

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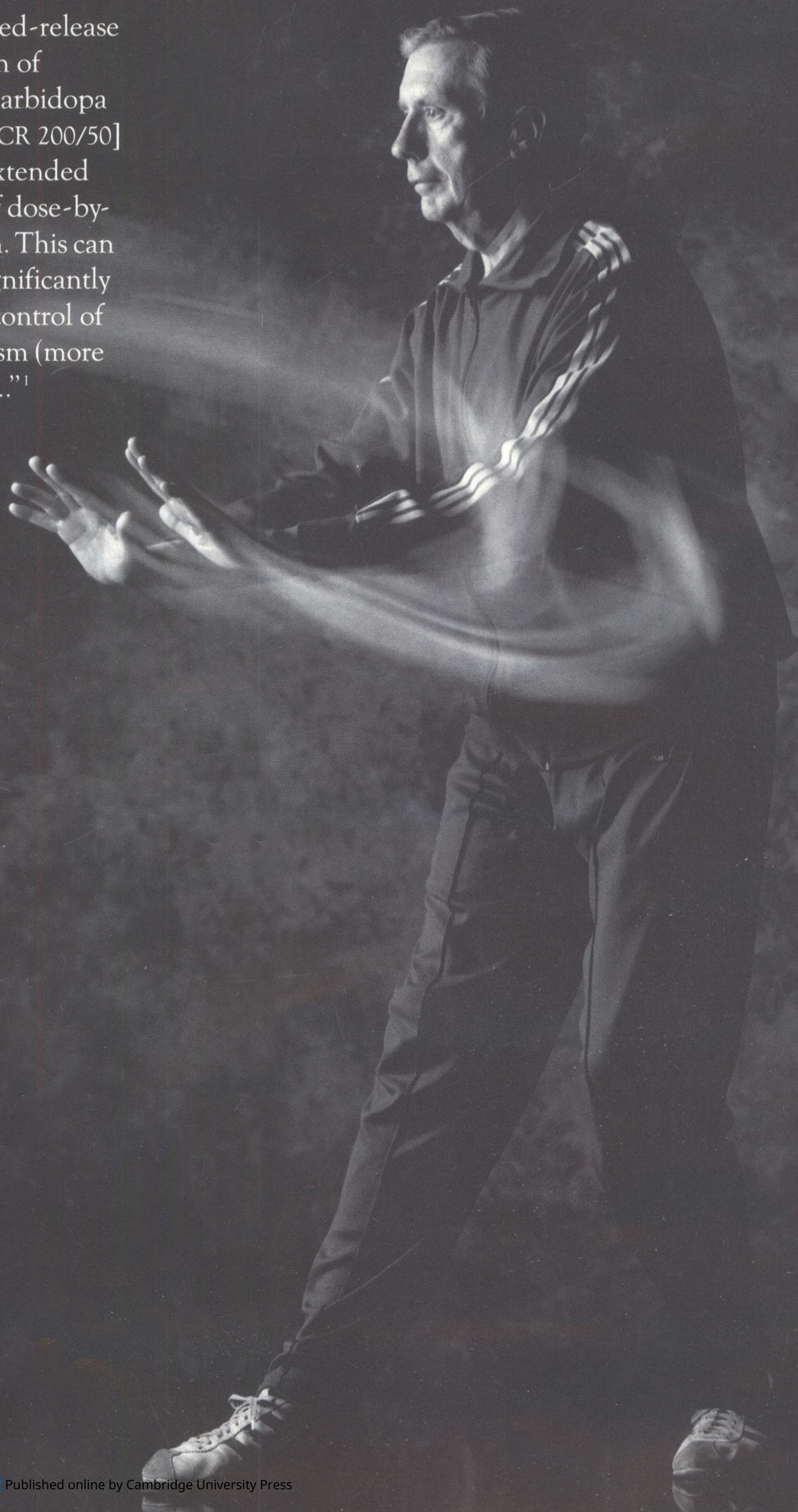
"A controlled-release formulation of levodopa/carbidopa [SINEMET® CR 200/50] offers an extended duration of dose-by-dose action. This can result in significantly improved control of Parkinsonism (more "on" time)..."[1]



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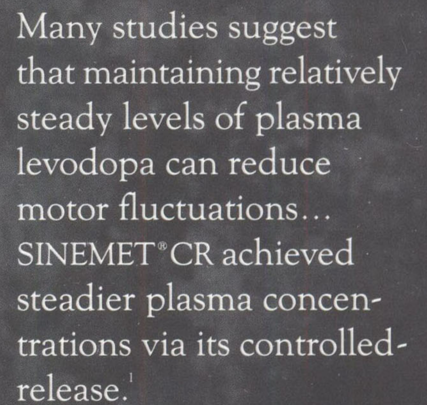

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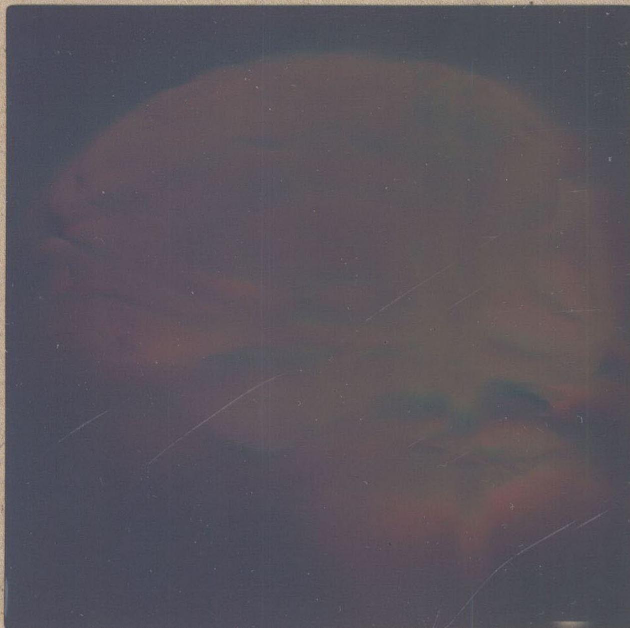
NEW CONTROLLED-RELEASE

Sinemet® CR

(levodopa/carbidopa) For the treatment of Parkinson's disease.

BRINGING
BACK
CONTROL



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PHARMA

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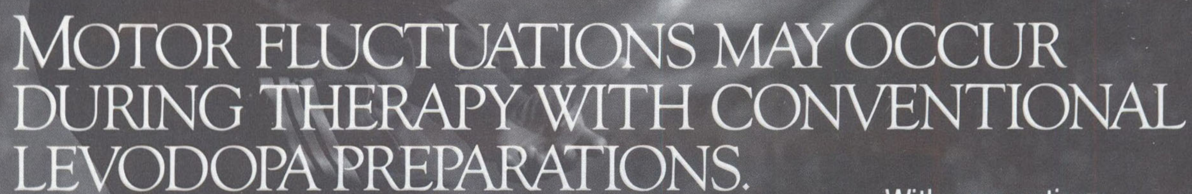

MOTOR FLUCTUATIONS MAY OCCUR DURING THERAPY WITH CONVENTIONAL LEVODOPA PREPARATIONS.

With preparations containing levodopa, over a period of time an increasing number of parkinsonian patients develop fluctuations in motor performance and dyskinesias.

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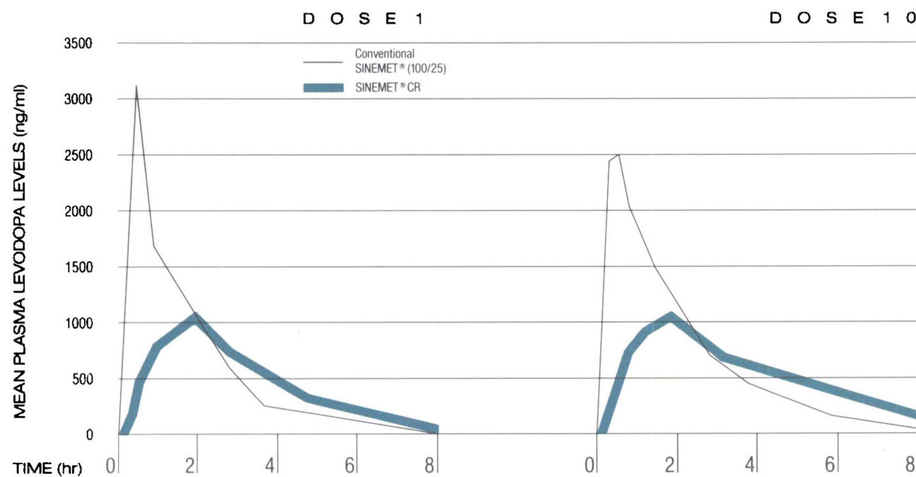
Why SINEMET® CR?

Smoother drug levels can reduce motor fluctuations.[2]

Smoother drug levels with SINEMET® CR.



Less fluctuation of plasma levodopa levels with SINEMET® CR vs. conventional SINEMET® in the same study group. Mean plasma levodopa concentrations after administration of two conventional tablets of SINEMET® 100/25, q8h for 10 doses, or one SINEMET® CR 200/50 tablet, q8h for 10 doses, in 12 healthy elderly subjects[3] (adapted).

SINEMET® CR offers more stability and control.

Releases carbidopa and levodopa as the tablet slowly dissolves.[4]

Continuous release of carbidopa and levodopa for up to six hours after a single dose.[4]

Smoother plasma levodopa levels aid reduction of "off" time.[4]

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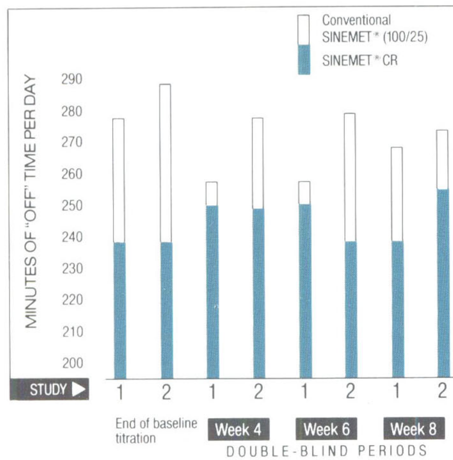
Patients can experience greater control with steadier levodopa levels.

New SINEMET® CR reduces "off" time in most patients.



Comparison of "off" times with conventional SINEMET® and SINEMET® CR. Results of 2 multiclinic studies[3] (adapted).

SINEMET® CR can provide relief of symptoms for all stages of Parkinson's disease.[1]

Helps attenuate "on-off" phenomenon.

Improves hours "on" and reduces "off" periods in most patients.[1]

Less variation in plasma levodopa levels and the peak plasma level is 60% lower than with conventional SINEMET®.[5] Helps prevent motor fluctuations.[1]

Less frequent dosing.

Well tolerated by most patients.

Effect of formulation: In controlled clinical trials, SINEMET® CR did not produce side effects that were unique to the controlled release formulation.

Reported side effects: The side effects most frequently reported (above 2%) were dyskinesia, nausea, hallucinations, confusion, dizziness, chorea, and dry mouth.

Sinemet® CR
(levodopa/carbidopa)

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℞ SINEMET® CR

(levodopa and carbidopa)

Controlled Release Tablets

Antiparkinson Agent

Clinical Pharmacology: SINEMET® CR (levodopa and carbidopa), a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor, is available in a polymer-based controlled-release tablet formulation. SINEMET® CR can be useful in reducing "off" time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had predictable peak dose dyskinesias and unpredictable motor fluctuations.

The symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. While the administration of dopamine is ineffective in the treatment of Parkinson's disease because it does not cross the blood-brain barrier, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier and is converted to dopamine in the basal ganglia. This is thought to be the mechanism whereby levodopa relieves the symptoms of Parkinson's disease.

Levodopa is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Carbidopa, a decarboxylase inhibitor, does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. Combined therapy with levodopa and carbidopa reduces the amount of levodopa required for optimum therapeutic benefit by about 75-80%, permits an earlier response to therapy, and also reduces the incidence of nausea, vomiting and cardiac arrhythmias. Combined therapy, however, does not decrease adverse reactions due to central effects of levodopa.

Following years of treatment with preparations containing levodopa, an increasing number of parkinsonian patients develop fluctuations in motor performance and dyskinesias. The advanced form of motor fluctuations ("on-off" phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

In clinical trials, patients with motor fluctuations experienced reduced "off" time with SINEMET® CR when compared with SINEMET®. Global ratings of improvement and activities of daily living in the "on" and "off" states, as assessed by both patient and physician, were slightly better in some patients during therapy with SINEMET® CR than with SINEMET®. In patients without motor fluctuations, SINEMET® CR provided therapeutic benefit similar to SINEMET® but with less frequent dosing.

Indications and Clinical Use: SINEMET® CR (levodopa and carbidopa) is indicated for the treatment of Parkinson's disease.

At this time, experience in patients not previously treated with levodopa/decarboxylase inhibitors or levodopa alone is limited.

SINEMET® CR is not recommended for the treatment of drug-induced extrapyramidal reactions.

Contraindications: Monoamine oxidase inhibitors (except low doses of selective MAO-B inhibitors) and SINEMET® CR (levodopa and carbidopa) should not be given concomitantly. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET® CR.

SINEMET® CR should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.

As with levodopa, SINEMET® CR should not be given when administration of a sympathomimetic amine is contraindicated.

SINEMET® CR is contraindicated in patients with known hypersensitivity to any component of this medication.

Because levodopa may activate a malignant melanoma, SINEMET® CR should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

Warnings: When patients are receiving levodopa monotherapy or SINEMET® (levodopa and carbidopa), this medication must be discontinued at least 8 hours before therapy with SINEMET® CR is started. (For appropriate dosage substitutions, see DOSAGE AND ADMINISTRATION).

As with levodopa or SINEMET®, SINEMET® CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. These adverse reactions may be more prolonged with SINEMET® CR than with SINEMET®. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET® CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Care should be exercised in administering SINEMET® CR to patients with a history of recent myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage administration and titration, in a facility with provisions for intensive cardiac care.

SINEMET® CR should be administered cautiously to patients with a history of peptic ulcer disease or of convulsions.

Precautions: *General:* Periodic evaluations of hepatic, hematopoietic, cardio-vascular and renal function are recommended during extended therapy (see ADVERSE REACTIONS).

Patients with chronic wide angle glaucoma may be treated cautiously with SINEMET® CR (levodopa and carbidopa), provided the intraocular pressure is well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Use in Children: Safety of SINEMET® CR in patients under 18 years of age has not been established.

Use in Pregnancy and Lactation: Although the effects of SINEMET® CR on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see TERATOLOGIC AND REPRODUCTIVE STUDIES). Therefore, use of SINEMET® CR in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to the mother and to the fetus. SINEMET® CR should not be given to nursing mothers.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET® CR:

Antihypertensive drugs: Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment of patients receiving antihypertensive drugs. Therefore, when therapy with SINEMET® CR is started, dosage adjustment of the antihypertensive drug may be required.

Psychoactive drugs: Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET® CR should be observed carefully for loss of therapeutic response.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricylic antidepressants and carbidopa-levodopa preparations. (For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.)

Other drugs: Although specific interaction studies were not performed with other concomitant drugs, in clinical trials of SINEMET® CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, thiazides, digoxin, H_2 antagonists, salicylates and other nonsteroidal anti-inflammatory drugs. SINEMET® CR was also used with other antiparkinson agents (see DOSAGE and ADMINISTRATION).

Adverse Reactions: In controlled clinical trials involving 748 patients with moderate to severe motor fluctuations, SINEMET® CR (levodopa and carbidopa) did not produce side effects which were unique to the controlled release formulation.

The adverse reaction reported most frequently was dyskinesia (12.8%). Occasionally, prolonged, and at times, severe afternoon dyskinesias have occurred in some patients.

Other adverse reactions that were reported frequently were: nausea (5.5%), hallucinations (5.3%), confusion (4.9%), dizziness (3.5%), headache (2.5%), depression (2.5%), chorea (2.5%), dry mouth (2.3%), somnolence (2.1%), dream abnormalities (2.1%), dystonia (2.0%) and asthenia (2.0%).

Adverse reactions occurring less frequently (less than 2%) were:

System	%
Body as a whole	
Chest pain	1.7
Fatigue	0.9
Weight loss	0.8
Cardiovascular	
Orthostatic hypotension	0.8
Palpitation	0.8
Hypotension	0.5
Nervous System / Psychiatric	
Insomnia	1.7
Falling	1.6
On-off phenomenon	1.2
Paresthesia	0.9
Disorientation	0.8
Anxiety disorders	0.8

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BRINGING BACK CONTROL

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Decreased mental acuity	0.7
Extrapyramidal disorder	0.7
Gait abnormalities	0.7
Agitation	0.5
Memory impairment	0.5
Gastrointestinal	
Anorexia	1.9
Constipation	1.5
Vomiting	1.3
Diarrhea	1.2
Gastrointestinal pain	0.9
Dyspepsia	0.8
Musculoskeletal	
Muscle cramps	0.9
Respiratory	
Dyspnea	1.6
Special Senses	
Blurred vision	1.1

Other adverse reactions that have been reported with levodopa or SINEMET® and may be potential side effects with SINEMET® CR are listed below:

Nervous System: Ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome.

Psychiatric: Sleepiness, euphoria, paranoid ideation and psychotic episodes, and dementia.

Cardiovascular: Arrhythmias, non-specific ECG changes, flushing, phlebitis.

Gastrointestinal: Bitter taste, sialorrhea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

Integumentary: Increased sweating, dark sweat, rash, hair loss.

Genitourinary: Urinary frequency, retention, incontinence, hematuria, dark urine, nocturia and priapism.

Special Senses: Diplopia, dilated pupils, oculogyric crises.

Miscellaneous: Weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, hypertension, neuroleptic malignant syndrome, malignant melanoma (see CONTRAINDICATIONS), leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

Convulsions have occurred; however, a causal relationship with levodopa or levodopa/carbidopa combinations has not been established.

Laboratory Tests: Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, and blood urea nitrogen.

Abnormalities in various laboratory tests have occurred with SINEMET® and may also occur with SINEMET® CR.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glycosuria.

Dosage and Administration: SINEMET® CR (levodopa and carbidopa) tablets contain a 4:1 ratio of levodopa to carbidopa (levodopa 200 mg/carbidopa 50 mg per tablet). The daily dosage of SINEMET® CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

SINEMET® CR may be administered as whole or as half tablets. To maintain the controlled release properties of the product, tablets should not be chewed or crushed.

Standard antiparkinson drugs, other than levodopa alone, may be continued while SINEMET® CR is being administered, although their dosage may have to be adjusted. The delayed onset of action with SINEMET® CR may require the supplemental use of conventional SINEMET® tablets for optimal control in the mornings.

Initial Dosage and Titration for Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations: Dosage with SINEMET® CR should be substituted at an amount that eventually provides approximately 10 to 30 percent more levodopa per day. The interval between doses should be prolonged by 30 to 50 percent. Initially, patients should receive SINEMET® CR at a dosage that provides the same amount of levodopa, but with a longer dosing interval. Depending on clinical response, the dosage may be increased.

A guide for the initiation of treatment with SINEMET® CR is shown in the following table:

Guideline for Initial Conversion from SINEMET® to SINEMET® CR

SINEMET® *Total Daily Dose** *Levodopa (mg)*	*SINEMET® CR (levodopa 200 mg/ carbidopa 50 mg) Suggested Dosage Regimen*
300-400	1 tablet b.i.d.
500-600	1 1/2 tablets b.i.d. or 1 tablet t.i.d.
700-800	A total of 4 tablets in 3 or more divided doses (e.g., 1 1/2 tablets a.m., 1 1/2 tablets early p.m., and 1 tablet later p.m.)
900-1000	A total of 5 tablets in 3 or more divided doses (e.g., 2 tablets a.m., 2 tablets early p.m., and 1 tablet later p.m.)

*For dosing ranges not shown in the table, see DOSAGE AND ADMINISTRATION.

Initial Dosage for Patients Currently Treated with Levodopa Alone: Levodopa must be discontinued at least eight hours before therapy with SINEMET® CR is started. SINEMET® CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET® CR two times daily.

Patients Without Prior Levodopa Therapy: Experience with SINEMET® CR is limited in the *de novo* parkinsonian patients. The initial recommended dose in patients with mild to moderate disease is 1 tablet of SINEMET® CR two times daily.

Titration: Doses and dosing intervals must be adjusted on an individual basis, depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided doses at intervals ranging from 4 to 12 hours during the waking day.

If the divided doses of SINEMET® CR are not equal, it is recommended that the smaller doses be given at the end of the day.

Maintenance: Because Parkinson's disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of SINEMET® CR may be required.

Addition of Other Antiparkinson Medications: Anticholinergic agents, dopamine agonists, amantadine and lower doses of selective MAO-B inhibitors can be given with SINEMET® CR. When combining therapies, dosage adjustments may be necessary.

Interruption of Therapy: Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET® CR is required, especially if the patient is receiving neuroleptics (see PRECAUTIONS).

If general anesthesia is required, SINEMET® CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

Availability of Dosage Form: No. 2041 - SINEMET® CR is peach-colored, oval-shaped, biconvex, scored compressed tablet, engraved SINEMET CR on one side and 521/521 on the other. Available in bottles of 100.

References: 1. LeWitt, P.A. et al.: Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): Clinical and pharmacokinetic studies, Neurology, 1989, Vol. 39, No. 11, Suppl. 2: 45-53. 2. Chase, T.A. et al.: Rationale for continuous dopaminomimetic therapy of Parkinson's disease, Neurology, 1989, Vol. 39, No. 11, Suppl. 2: 7-10. 3. Data on file; Merck Frosst Canada Inc., SINEMET® CR, Scientific information, 1988. 4. Dempski, R.E. et al.: Pharmaceutical design and development of a Sinemet controlled-release formulation, Neurology, 1989, Vol. 39, No. 11, Suppl. 2: 20-24. 5. Data on file; Merck Frosst Canada Inc., SINEMET® CR, Physicians Circular, 1990.

(352-a,5,91) 06-92-SCR-91-CDN-0003-M 2038E

PAAB

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Product Monograph
Available on Request

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℞LIORESAL®
(baclofen)
Muscle relaxant
Antispastic agent

INDICATIONS AND CLINICAL USES
Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Spina cord injuries and other spinal cord diseases.
CONTRAINDICATIONS
Hypersensitivity to LIORESAL.
WARNINGS
Abrupt Drug Withdrawal: Except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued to prevent visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, and worsening of spasticity.
Impaired Renal Function: Caution is advised in these patients and reduction in dosage may be necessary.
Stroke: Has not been of benefit and patients have shown poor tolerability to the drug.
Pregnancy and Lactation: Not recommended as safety has not been established. High doses in rats and rabbits are associated with an increase of abdominal hernias and ossification defects in the fetuses.
PRECAUTIONS
Not recommended in children under 12 as safety has not been established.
Because sedation may occur, caution patients regarding the operation of automobiles or dangerous machinery, activities made hazardous by decreased alertness, and use of alcohol and other CNS depressants.
Use with caution in spasticity that is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function, epilepsy or history of convulsive disorders (clinical state and EEG should be monitored), peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and patients receiving antihypertensive therapy.
ADVERSE REACTIONS
Most common adverse reactions are transient drowsiness; dizziness, weakness and fatigue. Others reported:
Neuropsychiatric: Headache, insomnia, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizures.
Cardiovascular: Hypotension, dyspnea, palpitation, chest pain, syncope.
Gastrointestinal: Nausea, constipation, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.
Genitourinary: Urinary frequency, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.
Other: Rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.
Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.
The following laboratory tests have been found to be abnormal in a few patients receiving LIORESAL: SGOT, alkaline phosphatase and blood sugar (all elevated).
SYMPTOMS AND TREATMENT OF OVERDOSAGE
Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures.
Co-administration of alcohol, diazepam, tricyclic anti-depressants, etc., may aggravate the symptoms.
Treatment: Treatment is symptomatic. In the alert patient, empty the stomach (induce emesis followed by lavage). In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis).
Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. Maintain high urinary output. Dialysis is indicated in severe poisoning associated with renal failure.
DOSAGE AND ADMINISTRATION
Optimal dosage of LIORESAL requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually 40-80 mg daily).
The following dosage titration schedule is suggested:
5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days
Total daily dose should not exceed a maximum of 20 mg q.i.d.
The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).
AVAILABILITY
LIORESAL (baclofen) 10 mg tablets: White to off-white flat-faced, oval tablets with GEIGY monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side.
LIORESAL D.S. 20 mg tablet: White to off-white capsule-shaped, biconvex tablets. Engraved GEIGY on one side and GW with bisect on the other.
Available in bottles of 100 tablets.
Product Monograph supplied on request.

References:
1. Cartlidge, N.E.F., Hudgson, P., Weightman, D.: A comparison of baclofen and diazepam in the treatment of spasticity. J Neurol. Sci. 23: 17-24 (1974).
2. Young, R., Delwaide, P.: Spasticity. New England Journal of Medicine 304: 28-33 & 96-99 (1981).
3. From, A., Heltberg, A.: A double blind trial with baclofen and diazepam in spasticity due to multiple sclerosis. Acta Neurol Scandinav. 51: 158-166, (1975).

See obc

Geigy
Mississauga, Ontario
L5N 2W5

PAAB CCPP

℞PROLOPA® 50/12.5
levodopa 50 mg benserazide 12.5 mg

Rx Summary
Antiparkinsonian Agent
Indications
Treatment of Parkinson's syndrome when not drug induced.
Contraindications
Known hypersensitivity to levodopa or benserazide; in patients in whom sympathomimetic amines are contraindicated; concomitantly with, or within 2 weeks of, MAOI administration; uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; narrow-angle glaucoma.
Warnings
Discontinue levodopa at least 12 hours before initiating 'Prolopa'. See Dosage section for substitution recommendations.
Not indicated in intention tremor, Huntington's chorea or drug-induced Parkinsonism.
Increase dosage gradually to avoid CNS side effects (involuntary movements). Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Caution in patients with history of psychotic disorders or receiving psychotherapeutic agents.
In patients with atrial, nodal or ventricular arrhythmias or history of myocardial infarction initiate treatment cautiously in hospital. Caution in patients with history of melanoma or suspicious undiagnosed skin lesions. Safety in patients under 18 years has not been established. In women who are or may become pregnant, weigh benefits against possible hazards to mother and fetus. Not recommended for nursing mothers.
Precautions
Monitor cardiovascular, hepatic, hematopoietic and renal function during extended therapy. Caution in patients with history of convulsive disorders. Upper gastrointestinal hemorrhage possible in patients with a history of peptic ulcer.
Normal activity should be resumed gradually to avoid risk of injury. Monitor intraocular pressure in patients with chronic wide-angle glaucoma. Pupillary dilation and activation of Horner's syndrome have been reported rarely. Exercise caution and monitor blood pressure in patients on anti-hypertensive medication. 'Prolopa' can be discontinued 12 hours prior to anesthesia. Observe patients on concomitant psychoactive drugs for unusual reactions.
Adverse Reactions
Most common are abnormal involuntary movements, usually dose dependent, which necessitate dosage reduction. Other serious reactions are periodic oscillations in performance (end of dose akinesia, on-off phenomena and akinesia paradoxica) after prolonged therapy, psychiatric disturbances (including paranoia, psychosis, depression, dementia, increased libido, euphoria, sedation and stimulation), and cardiovascular effects (including arrhythmias, orthostatic hypotension, hypertension, ECG changes and angina pectoris).
Neurologic, intellectual, gastrointestinal, dermatologic, hematologic, musculoskeletal, respiratory, genitourinary and ophthalmologic reactions have also been reported. Consult Product Monograph for complete list.
Dosage
Individualize therapy and titrate in small steps to maximize benefit without dyskinesias. Do not exceed the recommended dosage range.
Initially, one capsule 'Prolopa' 100-25 once or twice daily, increased carefully by one capsule every third or fourth day (slower in post-encephalitic Parkinsonism) until optimum therapeutic effect obtained without dyskinesias. At upper limits of dosage, increment slowly at 2-4 week intervals. Administer with food.
Optimal dosage is usually 4-8 'Prolopa' 100-25 capsules daily, in 4-6 divided doses.
'Prolopa' 200-50 capsules are intended for maintenance therapy once optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patient should receive more than 1000-1200 mg levodopa daily during the first year of treatment. 'Prolopa' 50-12.5 capsules should be used when frequent dosing is required to minimize adverse effects.
For patients previously treated with levodopa, **allow at least 12 hours to elapse** and initiate 'Prolopa' at 15% of previous levopoda dosage. During maintenance, reduce dosage slowly, if possible, to maximum of 600 mg levopoda daily.
Supply
'Prolopa' 50-12.5 capsules containing 50 mg levodopa and 12.5 mg benserazide. Contains mannitol.
'Prolopa' 100-25 capsules containing 100 mg levopoda and 25 mg benserazide.
'Prolopa' 200-50 capsules containing 200 mg levodopa and 50 mg benserazide.
Bottles of 100.
Product Monograph available on request.
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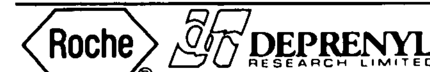

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® Epival*
divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

INDICATIONS AND CLINICAL USE Sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal; useful in primary generalized seizures with tonic-clonic manifestations. May also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

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.

CONTRAINDICTIONS Should not be administered to patients with hepatic disease or significant dysfunction. Contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Hepatic failures resulting in fatalities have occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first six months of treatment with valproic acid. A recent survey study of valproate use in the United States in nearly 400,000 patients between 1978 and 1984, has shown that children under two years of age who received the drug as part of multiple anticonvulsant therapy were at greatest risk (nearly 20-fold increase) of developing fatal hepatotoxicity. These patients typically had other medical conditions such as congenital metabolic disorders, mental retardation or organic brain disease, in addition to severe seizure disorders. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.

If Epival is to be used in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, the drug should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immmediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug. The frequency of adverse effects, particularly elevated liver enzymes, may increase with increasing dose. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of women receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid exposed women having children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida). Animal studies have demonstrated valproic acid induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs and an increased 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 2-to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anti-epileptics. Some reports indicate a possible similar association with the use of other anti-epileptic drugs, including trimethadione, paramethadione, and valproic acid. 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.

Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks 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 anti-epileptic medication is in doubt, appropriate consultation is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving Epival (divalproex sodium).

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of valproic acid greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment 1 fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of divalproex sodium and valproic acid on the development of the testes and on sperm production and fertility in humans is unknown.

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia and inhibition of platelet aggregation, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the drug should be discontinued.

Because Epival (divalproex sodium) may interact with other anti-epileptic drugs, periodic serum level determinations of concurrently administered anti-epileptics are recommended during the early part of therapy. (See DRUG INTERACTIONS.) There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Epival (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproic acid; the clinical significance of these is unknown.

Driving and Hazardous Occupations: 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: May potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. 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.

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

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

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

ADVERSE REACTIONS The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other anti-epileptics, 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 anti-epileptic 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 receiving valproic acid alone or in conjunction with phenobarbital.

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

Endocrine: There have been reports of irregular menses and secondary amenorrhea in patients receiving valproic acid.

Abnormal thyroid function tests have been reported (See PRECAUTIONS).

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

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (See PRECAUTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (eg. SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

Other: Edema of the extremities has been reported.

DOSAGE AND ADMINISTRATION The recommended initial dosage 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 maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 125 mg, it should be given in a divided regimen (See Table).

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by improving seizure control must be weighed against the increased incidence of adverse effects.

As the dosage is raised, blood levels of phenobarbital 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 tablets should be swallowed without chewing.**

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg: peach-coloured tablets of 250 mg; lavender-coloured tablets of 500 mg. Supplied in bottles of 100 tablets.

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

Weight		Total daily dose (mg)	Dosage (mg) Equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1,000	250	250	500
75-89.9	165-197.9	1,250	500	250	500

Product monograph available on request.

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Intermediate Prescribing Information

Tegretol® (carbamazepine)

TEGRETOL® 200 mg
TEGRETOL® CHEWTABS™ 100 mg and 200 mg
TEGRETOL® CR 200 mg and 400 mg

Indications

Symptomatic relief of pain of true or primary trigeminal neuralgia. Not for prophylactic use. Glossopharyngeal neuralgia has been relieved in some patients.

Management of psychomotor (temporal lobe) epilepsy. As an adjunct in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when combined with other antiepileptic agents.

As an alternative in patients with generalized tonic-clonic seizures and marked side effects or who fail to respond to other anticonvulsant drugs.

Ineffective for controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent generalization of epileptic discharge. Exacerbation of seizures may occur in patients with atypical absences.

Contraindications

History of hepatic disease or serious blood disorder, in patients with AV heart block *(see Precautions)*, hypersensitivity to carbamazepine or to tricyclic compounds.

Do not give with, or within 2 weeks of treatment with monoamine oxidase inhibitors.

Safe use in pregnancy has not been established. Do not administer in first 3 months of pregnancy. Do not give to women of childbearing potential unless benefits outweigh possible risks to the fetus. Avoid nursing while on TEGRETOL.

Warnings

Although infrequent, serious adverse effects have occurred during TEGRETOL use. Agranulocytosis and aplastic anemia have occurred in a few instances with fatal outcome. Leucopenia, thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis have occurred. Use TEGRETOL carefully with close clinical and laboratory supervision during treatment in order to detect signs and symptoms of blood dyscrasias.

Long-term toxicity studies in rats showed potential carcinogenic risk. Weigh possible risk of drug use against potential benefits before prescribing carbamazepine.

Precautions

Perform complete blood studies, including platelet counts, and evaluate hepatic and renal function and urinalysis before starting treatment. Maintain close clinical and laboratory supervision during treatment, including frequent complete blood counts. Discontinue TEGRETOL if signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur until case is reassessed.

Non-progressive or fluctuating asymptomatic leucopenia may occur and does not generally require TEGRETOL withdrawal. Discontinue TEGRETOL if the patient develops leucopenia which is progressive or accompanied by clinical symptoms.

Give TEGRETOL cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Monitor closely.

TEGRETOL may activate latent psychosis, or cause agitation or confusion, especially when used with other drugs. Use caution in alcoholic patients.

Use cautiously in patients with history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, perform an ECG to exclude patients with AV block.

Warn patients of possible hazards of operating machinery or driving automobiles due to possible dizziness and drowsiness with therapy.

Drug Interactions:

Hepatic enzyme induction by TEGRETOL may diminish activity of drugs metabolized in the liver.

Combined use of TEGRETOL with verapamil, diltiazem, erythromycin, troleandomycin, cimetidine, propoxyphene or isoniazid, can result in elevated plasma carbamazepine levels. Adapt carbamazepine dosage and monitor blood levels.

Concomitant use of carbamazepine and lithium may increase neurotoxic side effect risk.

Adapt dosage of anticoagulants to clinical needs whenever TEGRETOL is initiated or withdrawn.

TEGRETOL may decrease reliability of oral contraceptives. Advise patients to use alternative, non-hormonal method of contraception.

TEGRETOL may reduce alcohol tolerance; avoid alcohol during treatment.

Do not administer TEGRETOL in conjunction with MAO inhibitors. *(See Contraindications.)*

Adverse Reactions

Hematologic – Transitory leucopenia, eosinophilia, hyponatremia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia, aplastic anemia. In a few cases, deaths have occurred.

Hepatic – During long-term use, abnormal liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

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

Neurologic – Vertigo, somnolence, ataxia, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, increase in motor seizures. In rare cases, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, hyperacusis, and tinnitus. There have been reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to TEGRETOL could be established.

Cardiovascular – Thromboembolism, recurrence of thrombophlebitis in patients with prior history of thrombophlebitis, primary thrombophlebitis, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these effects (including myocardial infarction and arrhythmia) have been associated with other tricyclic agents.

Genitourinary – Urinary frequency, acute urinary retention, oliguria with elevated BP, azotemia, renal failure, impotence, elevation of BUN, albuminuria, glycosuria.

Respiratory – Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Gastrointestinal – Nausea, vomiting, gastric or abdominal discomfort, diarrhea or constipation, anorexia, dryness of the mouth and throat, glossitis, stomatitis.

Ophthalmic – There is no conclusive evidence that TEGRETOL produces pathological changes in the cornea, lens or retina. However, many phenothiazines and related drugs have been shown to cause eye changes. Periodic eye examinations, including slit-lamp fundoscopy and tonometry, are recommended.

Other: fever and chills, aching joints and muscles, leg cramps, conjunctivitis, adenopathy or lymphadenopathy.

Dosage and Administration

Epilepsy:

Take TEGRETOL tablets and CHEWTABS in 2-4 divided doses daily, with meals whenever possible.

Swallow TEGRETOL CR tablets (either whole or, if so prescribed, only half a tablet) unchewed with some liquid during or after meals. These should be prescribed as a twice-daily dosage. If needed, 3 divided doses may be prescribed.

Adults and Children Over 12 Years of Age:

Initially, 100-200 mg 1-2 times/day depending on severity of case and previous therapeutic history. Increase dose progressively, in divided doses, until best response obtained. Usual optimal dosage is 800-1200 mg/day. Rarely, some adults have received *1600 mg. Once seizures disappear and remain controlled,* reduce dose very gradually until minimum effective dose is reached.

Children 6-12 Years of Age:

Initially, 100 mg in divided doses on Day 1. Increase gradually by 100 mg/day until best response is obtained. Do not exceed 1000 mg/day. Once seizures disappear and remain controlled, reduce dose very gradually until minimum effective dose is reached.

Trigeminal Neuralgia:

Initially, 200 mg in 2 doses of 100 mg. Increase total daily dosage by 200 mg/day until pain relief is obtained. This usually occurs at 200-800 mg/day, but 1200 mg/day may be needed. Reduce dose progressively once pain relief is obtained and maintained, until minimal effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempt to reduce or discontinue TEGRETOL at intervals of not more than 3 months, *depending upon clinical course.*

Not for prophylactic use.

Availability

TEGRETOL Tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Bottles of 100 and 500 tablets.

TEGRETOL CHEWTABS 100 mg: Pale pink, round, flat, bevelled-edge tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each chewable tablet contains 100 mg carbamazepine. Bottles of 100 CHEWTABS.

TEGRETOL CHEWTABS 200 mg: Pale pink, oval biconvex tablets with distinct red spots. GEIGY engraved on one side and PU engraved on the other. Fully bisected between the P and U. Each chewable tablet contains 200 mg carbamazepine. Bottles of 100 CHEWTABS.

TEGRETOL CR 200 mg: Beige-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and HC/HC on the other. Fully bisected on both sides. Each controlled release tablet contains 200 mg carbamazepine. Bottles of 100 tablets.

TEGRETOL CR 400 mg: Brownish-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully bisected on both sides. Each controlled release tablet contains 400 mg carbamazepine. Bottles of 100 tablets.

Protect from heat and humidity.

Product Monograph available on request.

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PARLODEL® (bromocriptine mesylate)

Because quality of life is the issue

ACTIONS Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivate with D_2 type dopamine receptor agonist activity, *and has also* D_1 *dopamine receptor antagonist* properties. The dopaminomimetic activity of bromocriptine in the striatum is considered responsible for the clinical benefits seen in selected patients with Parkinson's disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication. Excessive dopaminomimetic drive may, however, provoke psychotic and other adverse reactions.

The extreme variability in G.I. tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

INDICATIONS* Parkinson's Disease: Parlodel (bromocriptine mesylate) has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylase inhibitor), in the symptomatic management of selected patients with Parkinson's disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and schedule of drug administration. Patients maintained on optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure may benefit from the concomitant use of Parlodel, by decreasing the occurrence and/or severity of these manifestations. Since rapid escala*tion of bromocriptine doses causes severe adverse reac*tions, it is recommended to combine a slow increase of Parlodel, usually with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine-treated *patients than in patients treated with levodopa. Parlodel is* not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's disease.

CONTRAINDICATIONS Other than sensitivity to ergot alkaloids, no absolute contraindications to treatment with Parlodel (bromocriptine mesylate) are known. For procedure during pregnancy see "Use in Pregnancy" under Precautions.

WARNINGS Long-term treatment (6-36 months) with Parlodel in doses of 20 to 100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. Where Parlodel was discontinued, these changes slowly reverted to normal.

PRECAUTIONS Parlodel (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with Parlodel; patients should therefore be cautioned against activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery, until their response has been determined.

Care should be exercised when administering Parlodel concomitantly with phenothiazines or antihypertensive agents. Due to drug interaction at the receptor site, dosage should be adjusted accordingly.

Alcohol should be avoided during treatment with Parlodel. In some patients, the concomitant use of Parlodel and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of Parlodel's possible adverse reactions.

Parlodel should always be taken with food. In cases where severe adverse effects, such as nausea, vomiting, vertigo or headaches are severe or persisting, the therapeutic *dosage of Parlodel should be reduced to half of one tablet* daily (1.25 mg) and increased gradually to that recommended. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in parkinsonian patients receiving Parlodel (see Drug Interactions).

As with all medication, Parlodel should be kept safely out of the reach of children.

Use in Pregnancy: If the patient wishes to become pregnant, Parlodel (bromocriptine mesylate) should be stopped as soon as possible after conception is suspected. In this event immunological confirmation should be done immediately. When pregnancy is confirmed, Parlodel, like all other drugs, should be discontinued unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus.

In human studies with Parlodel (reviewed by Turkalj, I.), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took Parlodel (bromocriptine mesylate) during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Use in Parkinson's Disease: Use of Parlodel (bromocriptine *mesylate), particularly in high doses, may be associated* with mental confusion and mental disturbances. Since patients with Parkinson's disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with Parlodel.

Parlodel administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of Parlodel may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following *discontinuation of Parlodel. Caution should be exercised* when administering Parlodel to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering Parlodel, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin may increase bromocriptine plasma levels.

Domperidone, a dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonise the therapeutically relevant prolactin lowering effect of Parlodel. It is possible that the antitumorigenic effect of Parlodel in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension which can, on rare occasions, lead to fainting and "shock-like" syndromes has been reported in sensitive patients. This is most likely to occur during the first few days of Parlodel treatment.

When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy were: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal *discomfort, visual disturbance, ataxia, insomnia, depression,* hypotension, shortness of breath, constipation and vertigo.

Less common adverse reactions include anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargia, mottling of skin, nasal stuffiness, nervousness, nightmares, parethesia, skin rash, urinary frequency, urinary incontinence, urinary retention and rarely signs or symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE There have been several reports of acute overdosage with Parlodel (bromocriptine mesylate) in children and adults. No life threatening reactions have occurred. Symptoms reported included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. Management is largely symptomatic; the cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION Parlodel (bromocriptine mesylate) should always be taken with food.

Although Parlodel (bromocriptine mesylate) has been found clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of Parlodel is one half of a 2.5 mg tablet (1.25 mg) at bedtime with food to establish initial tolerance. Thereafter, the recommended dosage is *2.5 mg daily in two divided doses, with meals, (half a 2.5 mg* tablet twice daily). The dosage may be increased very gradually, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually not exceed 2.5 mg. Clinical assessments are recommended at two week intervals or less during dosage titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40 mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around 10 mg daily or higher. During initial titration it is recommended that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

AVAILABILITY
TABLETS each containing 2.5 mg bromocriptine, as mesylate, available in bottles of 100.
CAPSULES each containing 5 mg bromocriptine, as mesylate, available in bottles of 100.

**For information on other approved indications, please consult the Parlodel product monograph, available to physicians and pharmacists on request.*

Sandoz Canada Inc.
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IN EPILEPSY *add* Frisium® 10 mg (clobazam) TO ACHIEVE SEIZURE CONTROL

Frisium (clobazam) Tablets, 10 mg
THERAPEUTIC CLASSIFICATION Anticonvulsant for adjunctive therapy. **ACTIONS** Frisium (clobazam) is a 1,5-benzodiazepine with anti-convulsant properties. In general, the mode of anti-epileptic action of clobazam is probably largely analogous to that of the 1,4-benzodiazepines. The differences between clobazam (a 1,5-benzodiazepine) and the 1,4-benzodiazepines in terms of therapeutic efficacy and neuro-toxicity are possibly due to the variation in degree of the agonist action at the high affinity benzodiazepine receptor or to differing relative action at the high and low affinity benzodiazepine receptors. Regarding the mechanism of action, it is likely that modifications to the function of gamma-aminobutyric acid (GABA) as an important inhibitory neurotransmitter underlie the pharmacological effects of the benzodiazepines. Electro-physiologic studies have shown that benzodiazepines potentiate GABA-ergic transmission at all levels of the neuroaxis, including the spinal cord, hypothalamus, hippocampus, *substantia nigra, cerebellar cortex and cerebral cortex. The changes* induced by the interaction of GABA with its receptors is enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain. The oral absorption of clobazam, like that of all benzodiazepines, is fast and complete. The time to peak concentration ranges from 1 to 4 hours. The administration of food with the drug has variable effects on the rate of absorption. The drug is highly lipophilic and is rapidly distributed in fat and cerebral gray matter. Within 1 to 4 hours of administration it has accumulated in *white matter and is then redistributed widely. The volume of distribution* is large. Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. Clobazam forms a number of metabolites with N-desmethylclobazam being the most important. The half-life of N-desmethylclobazam is much longer (mean 42 hours; range 36-46 hours) than for clobazam (mean 18 hours; range 10-30 hours). N-desmethylclobazam reaches higher serum levels, especially with long term administration of clobazam. The half-life increases with the patient's age. The drug is about 85% protein-bound; hepatic disease *may alter both the metabolism of the drug and its protein binding thus* affecting plasma clobazam levels. There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethylclobazam to clobazam efficacy. Most reports indicate there is no, or only a very weak, correlation between the clobazam dose, or blood levels, and its clinical effects. Therapeutic blood levels for clobazam are in the range of 50ng - 300ng/mL with the corresponding range for N-desmethylclobazam being from 1000 - 4000ng/mL. The serum levels at which anti-convulsant effects can be expected are not *yet known but it can be assumed that the therapeutic range lies in the* order of the figures given above. Since N-desmethylclobazam blood levels are 10-20 times higher than those for clobazam, and this metabolite also has anti-epileptic effects, it may be more important to the anti-epileptic efficacy of clobazam than the parent compound itself. After oral administration of ^{14}C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. Seven double-blind studies have been reported in which clobazam was given as adjunctive therapy versus placebo within an established anti-epileptic *regimen; clobazam was shown to be significantly superior to placebo.* **INDICATIONS** Frisium (clobazam) has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anti-convulsant therapy. **CONTRA-INDICATIONS** Hypersensitivity to clobazam, severe muscle weakness (myasthenia gravis) and narrow angle glaucoma. **WARNINGS Use in the elderly:** Frisium (clobazam) should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose. [See Precautions]. ***Potentiation of drug effects:*** *Patients should be cautioned about the* possibility of additive effects when Frisium is combined with alcohol or other drugs with central nervous system depressant effects. Patients should be advised against consumption of alcohol during treatment with Frisium. [See Precautions]. **Physical and psychological dependence:** Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer Frisium to individuals with a history of drug misuse or those who may increase the dose on their own initiative. *Such patients must be placed under careful surveillance. Signs and* symptoms of withdrawal may follow discontinuation of use of Frisium; thus it should not be abruptly discontinued after prolonged use. [See Precautions]. **Use in pregnancy:** Frisium should not be used in the first trimester of pregnancy and thereafter only if strictly indicated. Nursing mothers in whom therapy with Frisium is indicated should cease breast-feeding, since clobazam passes into breast milk. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If Frisium is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant. **Anterograde amnesia:** Anterograde amnesia is known to occur after administration of benzodiazepines. **Use in patients with depression or psychosis:** Frisium is not recommended for use in patients with depressive disorders or psychosis. **PRECAUTIONS Driving and Hazardous Activities:** Frisium (clobazam) possesses a mild central nervous system depressant effect, therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy. **Use in the Elderly:** *Elderly and debilitated patients, or those with organic brain* syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse *reactions.* ***Dependence Liability:*** *Frisium should not be administered to* individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, Frisium should be withdrawn gradually. **Tolerance:** Loss of part or all of the anti-convulsant effectiveness of clobazam has *been described in patients who have been receiving the drug for some* time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development. The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur. **Use in Mental and Emotional Disorders:** It should be recognized that suicidal tendencies may be present in patients with emotional *disorders; particularly those depressed. Protective measures and* appropriate treatment may be necessary and should be instituted without delay. Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, Clobazam should not be used in patients suspected of having psychotic tendencies. **Use in Patients with Impaired Renal or Hepatic Function:** Clobazam requires dealkylation and hydroxylation before conjugation. Usual precautions should be taken if Frisium is used in patients who may have some impairment of renal or hepatic function. It is suggested *that the dose in such cases be carefully titrated. In patients for whom* prolonged therapy with Frisium is indicated, blood counts and liver function should be monitored periodically. **Use in Patients with Acute, Severe Respiratory Insufficiency:** In patients with acute, severe respiratory insufficiency, respiratory function should be monitored. **Laboratory Tests:** If Frisium is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable. **Drug Interactions:** Most studies of the potential interactions of clobazam with other anti-epileptic agents have failed to demonstrate *significant interactions with phenytoin, phenobarbital, or* carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur. Alcohol may also significantly increase plasma clobazam levels. **Several of the established anti-epileptic agents:** *carbamazepine, diphenylhydantoin, phenobarbital, valproic acid, cause* the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethylclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenylhydantoin. **Toxicologic Studies:** In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver. (See Carcinogenicity) The relevance of these findings to man has not been established. **ADVERSE REACTIONS** From 19 published studies of Frisium (clobazam) use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects. The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%): $p<0.05$, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]) while other effects occurred *at a less than 1% incidence. Symptoms of tiredness may sometimes* appear, especially at the beginning of treatment with Frisium and when higher doses are used. Also in rare instances and usually only temporarily, the patient may experience dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, disorientation, tiredness, or a fine tremor of the fingers, but also paradoxical reactions, e.g., restlessness and irritability. After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly *in elderly patients; it sometimes persisted for some length of time.* Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, the drug may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. As with other drugs of this type (benzodiazepines), the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Isolated *cases of skin reactions such as rashes or urticaria have been observed.* **SYMPTOMS AND TREATMENT OF OVERDOSAGE Symptoms:** The cardinal manifestations are drowsiness, confusion, reduced reflexes, increasing sedation, and coma. Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and overstimulation usually when the effects of the drug begin to wear off. **Treatment:** Immediate gastric lavage may be beneficial if performed soon after ingestion of Frisium (clobazam). Given the route of excretion, [see 'ACTIONS' Section] forced diuresis by *short acting 'loop' diuretic may be useful some hours post-ingestion. If* respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. Respirations, pulse and blood pressure should be monitored. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of intravenous fluids started. Hypotension and central nervous system depression are managed by the usual means. **DOSAGE AND ADMINISTRATION** As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy *in the course of treatment must be borne in mind. In patients with* impaired liver and kidney function, Frisium (clobazam) should be used in reduced dosage. **Adults:** Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary. **Children:** In infants (<2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day. As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that Frisium be gradually reduced in dose *before treatment is discontinued.* ***Administration:*** *If the daily dose is* divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night. **DOSAGE FORM Composition:** Frisium (clobazam) tablets, 10 mg contain clobazam as active ingredient; Lactose, USP; Starch (Corn), NF; Talc, USP; Colloidal Silicon Dioxide, NF; and Magnesium Stearate, NF. **Storage Conditions:** Frisium tablets should be stored in their original containers at room temperature, below 25°C. **Availability:** Frisium is available as white, uncoated, bevelled, round tablets of 7 mm diameter, marked with 'BGL' above and below the scorebreak on the obverse and the Hoechst 'Tower and Bridge' logo on the reverse. Frisium 10 mg tablets are packaged in blisters of PVC film and aluminium foil and are distributed in packs of 30 [3x10] tablets.

Product Monograph available on request.

References:

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See pages iii, ibc

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DOSAGE
- Daily doses up to 30 mg may be taken as a single dose at bedtime.

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TO ACHIEVE SEIZURE CONTROL

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* Please consult precautions statement in product monograph.

For brief prescribing information see page xxi

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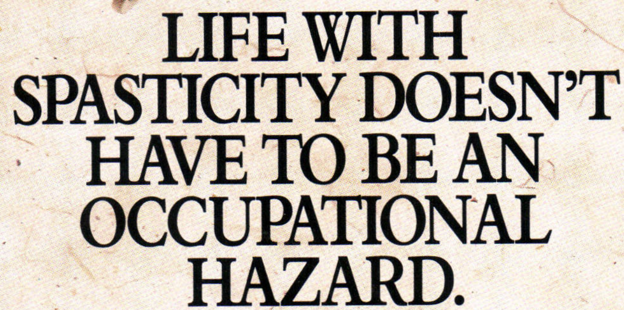

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