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. Data on file; Merck Frosst Canada Inc., SINEMET® CR, Scientific information, 1988. 3. Data on file; Merck Frosst Canada Inc., SINEMET® CR, Physicians Circular, 1990.

Product Monograph Available on Request

(352-a,5,91) 12-92-SCR-92-CDN-0021-JA

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https://doi.org/10.1017/S0317167100119882 Published online by Cambridge University Press