PrSINEMET® CR 200/50 100/25

(levodopa/carbidopa) CONTROLLED-RELEASE

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, cardiovascular 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 tricyclic 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%, 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.

Hematologic: Leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

Miscellaneous: Weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, hypertension, neuroleptic malignant syndrome, malignant melanoma (see CONTRAINDICATIONS).

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.

Symptoms and Treatment of Overdosage: Management of acute overdosage with SINEMET© CR (levodopa and carbidopa) is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET© CR.

Electrocardiographic monitoring should be instituted and the patient observed carefully for the development of arrhythmias. If required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET© CR should be taken into consideration. To date, no experience has been reported with dialysis, hence, its value in overdosage is not known.

Dosage and Administration: SINEMET© CR (levodopa and carbidopa) Tablets contain a 4:1 ratio of levodopa to carbidopa. SINEMET© CR 200/50 contains levodopa 200 mg/carbidopa 50 mg per tablet. SINEMET© CR 100/25 contains levodopa 100 mg/carbidopa 25 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 200/50 may be administered as whole or as half tablets. SINEMET© CR 100/25 should only be administered as whole 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 200/50 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 200/50 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 200/50 is shown in the following table.

Guideline for Initial Conversion from SINEMET© to SINEMET© CR 200/50

SINEMET© Total Daily Dose Levodopa (mg)*	*SINEMET© CR 200/50 (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.

SINEMET© CR 100/25 is available to facilitate titration when 100 mg steps are required and as an alternative to the half tablet of SINEMET© CR 200/50.

Initial Dosage for Patients Currently Treated with Levodopa Alone: Levodopa must be discontinued at least eight hours before therapy with SINEMET© CR 200/50 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 200/50 two times daily.

Patients Without Prior Levodopa Therapy: Experience with SINEMET© CR is limited in the *de novo* parkinsonian patients.

SINEMET© CR 100/25 may be used in early stage patients who have not had prior levodopa therapy or to facilitate titration when necessary in patients receiving SINEMET© CR 200/50. The initial recommended dose is 1 tablet of SINEMET© CR 100/25 twice daily. For patients who require more levodopa, a daily dose of 1 to 4 tablets of SINEMET© CR 100/25 twice a day is generally well-tolerated.

When appropriate, levodopa therapy may also be initiated with SINEMET© CR 200/50. The initial recommended dose in patients with mild to moderate disease is 1 tablet of SINEMET© CR 200/50 two times daily. Initial dosages should not exceed 600 mg per day of levodopa or be given at intervals of less than 6 hours.

If the divided doses of SINEMET® CR 200/50 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.

Pharmaceutical Information

I. Drug Substance

Proper name. levodopa and carbidopa

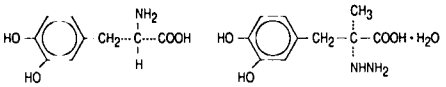
Chemical name.

Levodopa	*Carbidopa*
(-)-3-(3,4-Dihydroxphenyl)-L-alanine	(-)-L-α–Hydrazino-3,4-dihydroxy-α-methyl-hydrocinnamic acid monohydrate.

Empirical formula.

$C_9H_{11}NO_4$	$C_{10}H_{14}N_2O_4 \bullet H_2O$

Structural formula:



Molecular weight:

197.2	244.3

Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3

Description

Levodopa, an aromatic amino acid, is a white crystalline compound, slightly soluble in water	Carbidopa, an inhibitor of aromatic amino acid decarboxylase is a white, crystalline compound, slightly soluble in water.

II Composition

SINEMET® CR is a controlled-release formulation of levodopa and carbidopa, in a ratio of 4:1. The tablet contains a polymer-based drug delivery system which controls the release of levodopa and carbidopa as it slowly erodes. Excipients include hydroxypropyl cellulose, NF and magnesium stearate, NF. SINEMET® CR 100/25 Tablets contain red ferric oxide, NF. SINEMET® CR 200/50 Tablets contain red ferric oxide, NF and D&C Yellow No. 10.

III Storage Recommendations

Store between 15°C (59°F) and 30°C (86°F). Protect from sunlight.

Availability of Dosage Forms: No. 2042 - SINEMET® CR 100/25 is a pink-colored, oval-shaped, biconvex, compressed tablet, engraved SINEMET CR on one side and 601 on the other. Available in bottles of 100.

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.

Product Monograph Available on Request

(384-a,4,93) 04-94-SCR-93-CDN-0040-JA

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