

SINEMET[®] CR

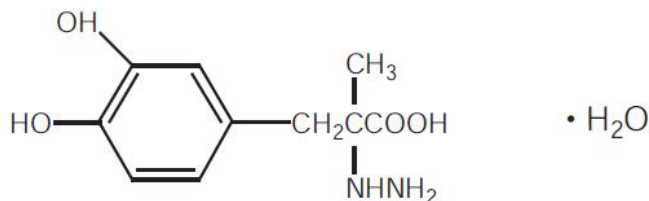
(carbidopa levodopa)

Sustained-Release Tablets

DESCRIPTION

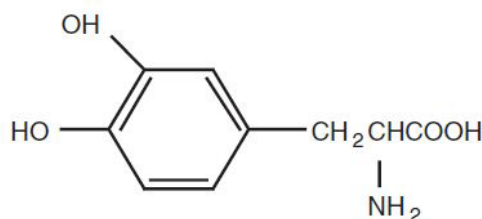
SINEMET[®] CR (carbidopa levodopa) is a sustained-release combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (—)-L- α -hydrazino- α -methyl- β -(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is C₁₀H₁₄N₂O₄•H₂O, and its structural formula is:



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

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (—)-L- α -amino- β -(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is C₉H₁₁NO₄, and its structural formula is:



SINEMET CR is supplied as sustained-release tablets containing either 50 mg of carbidopa and 200 mg of levodopa, or 25 mg of carbidopa and 100 mg of levodopa. Inactive ingredients are hydroxypropyl cellulose, magnesium stearate, and hypromellose. SINEMET CR 25-100 and SINEMET CR 50-200 also contain FD&C Blue #2/Indigo Carmine AL and FD&C Red #40/Allura Red AC AL.

The 50-200 tablet is supplied as an oval, compressed tablet that is dappled-purple in color and is coded "521" on one side and plain on the other. The 25-100 tablet is supplied as an oval, compressed tablet that is dappled-purple in color and is coded "601" on one side and plain on the other. The SINEMET CR tablet is a polymeric-based drug delivery system that controls the release of carbidopa and levodopa as it slowly erodes. SINEMET CR 25-100 is available to facilitate titration when 100 mg steps are required.

CLINICAL PHARMACOLOGY

Mechanism of Action

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease

apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Pharmacodynamics

When levodopa is administered orally, it 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 accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It 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.

Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, and akinesia. 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, in some patients they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

SINEMET CR contains either 50 mg of carbidopa and 200 mg of levodopa, or 25 mg of carbidopa and 100 mg of levodopa in a sustained-release dosage form designed to release these ingredients over a 4- to 6-hour period. With SINEMET CR there is less variation in plasma levodopa levels than with SINEMET® (carbidopa levodopa) immediate release tablets, the conventional formulation. *However, SINEMET CR is less systemically bioavailable than SINEMET and may require increased daily doses to achieve the same level of symptomatic relief as provided by SINEMET.*

In clinical trials, patients with moderate to severe motor fluctuations who received SINEMET CR *did not experience quantitatively significant reductions* in 'off' time when compared to SINEMET. However, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET. In patients without motor fluctuations, SINEMET CR, under controlled conditions, provided the same therapeutic benefit with less frequent dosing when compared to SINEMET.

Pharmacokinetics

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

Elimination half-life of levodopa in the presence of carbidopa is about 1.5 hours. Following SINEMET CR, the apparent half-life of levodopa may be prolonged because of continuous absorption.

In healthy elderly subjects (56-67 years old) the mean time-to-peak concentration of levodopa after a single dose of SINEMET CR 50-200 was about 2 hours as compared to 0.5 hours after standard SINEMET. The maximum concentration of levodopa after a single dose of SINEMET CR was about 35% of the standard SINEMET (1151 vs. 3256 ng/mL). The extent of availability of levodopa from SINEMET CR was about 70-75% relative to intravenous levodopa or standard SINEMET in the elderly. The absolute bioavailability of levodopa from SINEMET CR (relative to I.V.) in young subjects was shown to be only about 44%. The extent of availability and the peak concentrations of levodopa were comparable in the elderly after a single dose and at steady state after t.i.d. administration of SINEMET CR 50-200. In elderly subjects, the average trough levels of levodopa at steady state after the CR tablet were about 2 fold higher than after the standard SINEMET (163 vs. 74 ng/mL).

In these studies, using similar total daily doses of levodopa, plasma levodopa concentrations with SINEMET CR fluctuated in a narrower range than with SINEMET. Because the bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70-75%, the daily dosage of levodopa necessary to produce a given clinical response with the sustained-release formulation will usually be higher.

The extent of availability and peak concentrations of levodopa after a single dose of SINEMET CR 50-200 increased by about 50% and 25%, respectively, when administered with food.

At steady state, the bioavailability of carbidopa from SINEMET Tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa. At steady state, carbidopa bioavailability from SINEMET CR 50-200 is approximately 58% relative to that from SINEMET.

Pyridoxine hydrochloride (vitamin B₆), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

Special Populations

Geriatric: A study in eight young healthy subjects (21-22 yr) and eight elderly healthy subjects (69-76 yr) showed that the absolute bioavailability of levodopa was similar between young and elderly subjects following oral administration of levodopa and carbidopa. However, the systemic exposure (AUC) of levodopa was increased by 55% in elderly subjects compared to young subjects. Based on another study in forty patients with Parkinson's disease, there was a correlation between age of patients and the increase of AUC of levodopa following administration of levodopa and an inhibitor of peripheral dopa decarboxylase. AUC of levodopa was increased by 28% in elderly patients (≥ 65 yr) compared to young patients (< 65 yr). Additionally, mean value of C_{max} for levodopa was increased by 24% in elderly patients (≥ 65 yr) compared to young patients (< 65 yr) (see PRECAUTIONS, *Geriatric Use*).

The AUC of carbidopa was increased in elderly subjects (n=10, 65-76 yr) by 29% compared to young subjects (n=24, 23-64 yr) following IV administration of 50 mg levodopa with carbidopa (50 mg). This increase is not considered a clinically significant impact.

INDICATIONS AND USAGE

SINEMET CR is indicated in the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (see PRECAUTIONS, *Drug Interactions*).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug, and in patients with narrow-angle glaucoma.

WARNINGS

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least twelve hours before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See DOSAGE AND ADMINISTRATION section before initiating therapy.

SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse central nervous system (CNS) effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with SINEMET CR than with levodopa alone.

Patients receiving SINEMET CR may develop increased dyskinesias compared to SINEMET. Dyskinesias are a common side effect of carbidopa levodopa treatment. The occurrence of dyskinesias may require dosage reduction.

All patients should be observed carefully for the development of depression with concomitant suicidal tendencies.

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of 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 adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Vitamin B₆ Deficiency and Seizures

Treatment with SINEMET CR may contribute to reduced vitamin B₆ levels. Higher doses of carbidopa/levodopa may increase the risk of vitamin B₆ deficiency. Seizures associated with vitamin B₆ deficiency have been reported in the postmarketing setting in patients taking SINEMET CR. In these reported cases, seizures were refractory to traditional anti-seizure medications and only resolved after vitamin B₆ administration. Other symptoms of vitamin B₆ deficiency may occur, including depression, confusion, cheilosis, glossitis, dermatitis, anemia, and/or neuropathy. Evaluate vitamin B₆ levels prior to initiation of SINEMET CR and periodically while on treatment or if symptoms associated with vitamin B₆ deficiency are identified. Supplement with vitamin B₆ as necessary.

Falling Asleep During Activities of Daily Living and Somnolence

Patients taking SINEMET CR alone or with other dopaminergic drugs have reported suddenly falling asleep without prior warning of sleepiness while engaged in activities of daily living (includes operation of motor vehicles). Road traffic accidents attributed to sudden sleep onset have been reported. Although many patients reported somnolence while on dopaminergic medications, there have been reports of road traffic accidents attributed to sudden onset of sleep in which the patient did not perceive any warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Sudden onset of sleep has been reported to occur as long as one year after the initiation of treatment.

Falling asleep while engaged in activities of daily living usually occurs in patients experiencing pre-existing somnolence, although some patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving or operating machines during treatment with SINEMET CR. Patients who have already experienced somnolence or an episode of sudden sleep onset should not participate in these activities during treatment with SINEMET CR.

Before initiating treatment with SINEMET CR, advise patients about the potential to develop drowsiness and ask specifically about factors that may increase the risk for somnolence with SINEMET CR such as the use of concomitant sedating medications and the presence of sleep disorders. Consider discontinuing SINEMET CR in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.). If treatment with SINEMET CR continues, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hyperpyrexia and Confusion

Sporadic cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in association with dose reductions or withdrawal of certain antiparkinsonian agents such as levodopa, carbidopa levodopa and carbidopa levodopa extended release. Therefore, patients should be observed carefully when the dosage of levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS; however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

General

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

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

Dyskinesia

Levodopa alone, as well as SINEMET CR, is associated with dyskinesias. The occurrence of dyskinesias may require dosage reduction.

Hallucinations / Psychotic-Like Behavior

Hallucinations and psychotic-like behavior have been reported with dopaminergic medications. In general, hallucinations present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Hallucinations may be accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming.

SINEMET CR may have similar effects on thinking and behavior. This abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Ordinarily, patients with a major psychotic disorder should not be treated with SINEMET CR, because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of SINEMET CR.

Impulse Control / Compulsive Behaviors

Reports of patients taking dopaminergic medications (medications that increase central dopaminergic tone), suggest that patients may experience an intense urge to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or the caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with SINEMET CR. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking SINEMET CR (see Information for Patients).

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased

risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using SINEMET CR for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Information for Patients

The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa levodopa which releases these ingredients over a 4- to 6-hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

Patients should be advised that, occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of SINEMET CR. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be informed that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multivitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa or carbidopa levodopa therapy.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

Patients should be alerted to the possibility of sudden onset of sleep during daily activities, in some cases without awareness or warning signs, when they are taking dopaminergic agents, including levodopa. Patients should be advised to exercise caution while driving or operating machinery and that if they have experienced somnolence and/or sudden sleep onset, they must refrain from these activities. (See WARNINGS, Falling Asleep During Activities of Daily Living and Somnolence.)

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including SINEMET CR. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with SINEMET CR. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking SINEMET CR. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking SINEMET CR. (see PRECAUTIONS, *Impulse Control / Compulsive Behaviors*.)

Inform patients that vitamin B₆ deficiency may develop during treatment with carbidopa/levodopa therapies, including SINEMET CR. Tell patients to inform their healthcare provider if they develop symptoms such as depression, confusion, cheilosis, glossitis, dermatitis, anemia, neuropathy, and/or seizures (see WARNINGS, *Vitamin B₆ Deficiency and Seizures*).

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase (LDH), and bilirubin. Abnormalities in blood urea nitrogen (BUN) and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa levodopa preparations than with levodopa.

Carbidopa levodopa preparations, such as SINEMET and SINEMET CR, 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 glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or carbidopa levodopa therapy.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR.

Symptomatic postural hypotension has occurred when carbidopa levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required.

For patients receiving MAO inhibitors (Type A or B), see CONTRAINDICATIONS. Concomitant therapy with selegiline and carbidopa levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa levodopa alone (see CONTRAINDICATIONS).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa levodopa preparations.

Dopamine D₂ receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, 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 carefully observed for loss of therapeutic response.

Use of SINEMET CR with dopamine-depleting agents (e.g., reserpine and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

SINEMET CR and iron salts or multivitamins containing iron salts should be coadministered with caution. Iron salts can form chelates with levodopa and carbidopa and consequently reduce the bioavailability of carbidopa and levodopa.

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year bioassay of SINEMET, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy

No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET. There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers

Levodopa has been detected in human milk. Caution should be exercised when SINEMET CR is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended.

Geriatric Use

In the clinical efficacy trials for SINEMET, almost half of the patients were older than 65, but few were older than 75. No overall meaningful differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals to adverse drug reactions such as hallucinations cannot be ruled out. There is no specific dosing recommendation based upon clinical pharmacology data as SINEMET and SINEMET CR are titrated as tolerated for clinical effect.

ADVERSE REACTIONS

In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on SINEMET were randomized to therapy with either SINEMET or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET, as shown in Table 1.

Table 1: Clinical Adverse Experiences Occurring in 1% or Greater of Patients

Adverse Experience	SINEMET CR	SINEMET
	n=491 %	n=524 %
Dyskinesia	16.5	12.2
Nausea	5.5	5.7
Hallucinations	3.9	3.2
Confusion	3.7	2.3
Dizziness	2.9	2.3
Depression	2.2	1.3
Urinary tract infection	2.2	2.3
Headache	2.0	1.9
Dream abnormalities	1.8	0.8
Dystonia	1.8	0.8
Vomiting	1.8	1.9
Upper respiratory infection	1.8	1.0
Dyspnea	1.6	0.4
'On-Off' phenomena	1.6	1.1
Back pain	1.6	0.6
Dry mouth	1.4	1.1
Anorexia	1.2	1.1
Diarrhea	1.2	0.6
Insomnia	1.2	1.0
Orthostatic hypotension	1.0	1.1
Shoulder pain	1.0	0.6
Chest pain	1.0	0.8
Muscle cramps	0.8	1.0
Paresthesia	0.8	1.1
Urinary frequency	0.8	1.1
Dyspepsia	0.6	1.1
Constipation	0.2	1.5

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET during controlled clinical trials included:

decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Body as a Whole

Asthenia, fatigue, abdominal pain, orthostatic effects.

Cardiovascular

Palpitation, hypertension, hypotension, myocardial infarction.

Gastrointestinal

Gastrointestinal pain, dysphagia, heartburn.

Metabolic

Weight loss.

Musculoskeletal

Leg pain.

Nervous System/Psychiatric

Chorea, somnolence, falling, anxiety, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Respiratory

Cough, pharyngeal pain, common cold.

Skin

Rash.

Special Senses

Blurred vision.

Urogenital

Urinary incontinence.

Laboratory Tests

Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

The following adverse experiences have been reported in postmarketing experience with SINEMET CR:

Cardiovascular

Cardiac irregularities, syncope.

Gastrointestinal

Taste alterations, dark saliva.

Hypersensitivity

Angioedema, urticaria, pruritus, bullous lesions (including pemphigus-like reactions).

Nervous System/Psychiatric

Increased tremor, peripheral neuropathy, psychotic episodes including delusions and paranoid ideation, pathological gambling, increased libido including hypersexuality, impulse control symptoms, seizures (including convulsions).

Skin

Alopecia, flushing, dark sweat.

Urogenital

Dark urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa levodopa formulations and may occur with SINEMET CR are:

Cardiovascular

Phlebitis.

Gastrointestinal

Gastrointestinal bleeding, development of duodenal ulcer, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.

Hematologic

Hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.

Hypersensitivity

Henoch-Schönlein purpura.

Metabolic

Weight gain, edema.

Nervous System/Psychiatric

Ataxia, depression with suicidal tendencies, dementia, euphoria, bradykinetic episodes, numbness, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome, nightmares.

Skin

Malignant melanoma, increased sweating.

Special Senses

Oculogyric crises, mydriasis, diplopia.

Urogenital

Urinary retention, priapism.

Miscellaneous

Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns.

Laboratory Tests

Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), bilirubin, Coombs test, uric acid, vitamin B₆ levels.

OVERDOSAGE

Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed 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.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION

SINEMET CR contains carbidopa and levodopa in a 1:4 ratio as either the 50-200 tablet or the 25-100 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 involuntary movements, dyskinesias or nausea. SINEMET CR should not be chewed or crushed.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B₆).

Management of Vitamin B₆ Levels

Evaluate vitamin B₆ levels prior to initiating carbidopa/levodopa therapies including SINEMET CR, periodically during treatment, and as clinically indicated (see WARNINGS, *Vitamin B₆ Deficiency and Seizures*). If vitamin B₆ levels are low, supplement to sufficient levels per standard of care. Patients may initiate and continue treatment with SINEMET CR while supplementing vitamin B₆.

Initial Dosage

Patients currently treated with conventional carbidopa levodopa preparations: Studies show that peripheral dopa-decarboxylase is saturated by the bioavailable carbidopa at doses of 70 mg a day and greater. Because the bioavailabilities of carbidopa and levodopa in SINEMET and SINEMET CR are different, appropriate adjustments should be made, as shown in Table 2.

Table 2: Approximate Bioavailabilities at Steady State*

Tablet	Amount of Levodopa (mg) in Each Tablet	Approximate Bioavailability	Approximate Amount of Bioavailable Levodopa (mg) in Each Tablet
SINEMET CR 50-200	200	0.70-0.75 [†]	140-150
SINEMET 25-100	100	0.99 [‡]	99

* This table is only a guide to bioavailabilities since other factors such as food, drugs, and inter-patient variabilities may affect the bioavailability of carbidopa and levodopa.

[†] The extent of availability of levodopa from SINEMET CR was about 70-75% relative to intravenous levodopa or standard SINEMET in the elderly.

[‡] The extent of availability of levodopa from SINEMET was 99% relative to intravenous levodopa in the healthy elderly.

Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAGE AND ADMINISTRATION, *Titration with SINEMET CR*). The interval between doses of SINEMET CR should be 4-8 hours during the waking day. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

A guideline for initiation of SINEMET CR is shown in Table 3.

Table 3: Guidelines for Initial Conversion from SINEMET to SINEMET CR

SINEMET Total Daily Dose* <u>Levodopa (mg)</u>	SINEMET CR Suggested <u>Dosage Regimen</u>
300-400	200 mg b.i.d.
500-600	300 mg b.i.d. or 200 mg t.i.d.
700-800	A total of 800 mg in 3 or more divided doses (e.g., 300 mg a.m., 300 mg early p.m., and 200 mg later p.m.)
900-1000	A total of 1000 mg in 3 or more divided doses (e.g., 400 mg a.m., 400 mg early p.m., and 200 mg later p.m.)

*For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage — Patients currently treated with conventional carbidopa levodopa preparations*.

Patients currently treated with levodopa without a decarboxylase inhibitor: Levodopa must be discontinued at least twelve 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 50-200 b.i.d.

Patients not receiving levodopa: In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR 50-200 b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration with SINEMET CR

Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with doses of SINEMET CR that provide 400 to 1600 mg of levodopa per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses of SINEMET CR (2400 mg or more of levodopa per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance

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

Addition of Other Antiparkinson Medications

Anticholinergic agents, dopamine agonists, and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of carbidopa levodopa immediate release 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional immediate-release levodopa for a brief time during daytime hours.

Interruption of Therapy

Sporadic cases of hyperpyrexia and confusion have been associated with dose reductions and withdrawal of SINEMET or SINEMET CR.

Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS.)

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 patient should be observed for symptoms resembling NMS, and the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

No. 3919 — SINEMET CR 50-200 (carbidopa levodopa) Sustained-Release Tablets containing 50 mg of carbidopa and 200 mg of levodopa, are dappled-purple in color, oval, compressed tablets, that are coded "521" on one side and plain on the other. They are supplied as follows:

NDC - Pending

No. 3918 — SINEMET CR 25-100 (carbidopa levodopa) Sustained-Release Tablets containing 25 mg of carbidopa and 100 mg of levodopa, are dappled-purple in color, oval, compressed tablets, that are coded "601" on one side and plain on the other. They are supplied as follows:

NDC - Pending

Storage and Handling

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.

Dispense in a tightly closed, light-resistant container.

Distributed by: Organon LLC, a subsidiary of
 ORGANON & Co.,
Jersey City, NJ 07302, USA

For patent information: www.organon.com/our-solutions/patent/

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Revised: 3/2026

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