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SINEMET CR 50/200 Tablets

(carbidopa and levodopa)

SINEMET CR is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, in a polymer-based controlled-release tablet formulation, for use in the treatment of Parkinson's disease and syndrome. SINEMET CR is particularly useful to reduce "off" time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had predictable peak-dose dyskinesias and unpredictable motor fluctuations.

Patients with Parkinson's disease treated with preparations containing levodopa 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, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Levodopa relieves the symptoms of Parkinson's disease by being decarboxylated to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits only the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine. This normally obviates the necessity for large doses of levodopa at frequent intervals. The lower dosage reduces or may help eliminate gastrointestinal and cardiovascular side effects, especially those which are attributable to dopamine being formed in extracerebral tissues.

SINEMET CR is designed to release the active ingredients over a 4- to 6-hour period. With this formulation there is less variation in plasma levodopa levels and the peak plasma level is 60% lower than with conventional SINEMET.

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" state, as assessed by both patient and physician, were better during therapy with SINEMET CR than with SINEMET. Patients considered SINEMET CR to be more helpful for their clinical fluctuations, and preferred it over SINEMET. In patients without motor fluctuations, SINEMET CR, under controlled conditions, provided the same therapeutic benefit with less frequent dosing than with SINEMET.

DESCRIPTION

SINEMET CR is supplied as sustained-release tablets containing 50 mg of carbidopa and 200 mg of levodopa. Inactive ingredients are hydroxypropyl cellulose, magnesium stearate, and hypromellose. SINEMET CR 50-200 also contains 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.

INDICATIONS

- Idiopathic Parkinson's disease.
- Postencephalitic parkinsonism.
- Symptomatic parkinsonism (carbon monoxide or manganese intoxication).
- Patients with Parkinson's disease or parkinsonism who are taking vitamin preparations that contain pyridoxine.

- To reduce "off" time in patients previously treated with levodopa/decarboxylase inhibitor preparations, or with levodopa alone, who have had motor fluctuations characterized by end-of-dose deterioration ("wearing-off" phenomenon), peak dose dyskinesias, akinesia, or similar evidence of short-duration motor disturbances.

DOSAGE & ADMINISTRATION

SINEMET CR tablets contain a 1:4 ratio of carbidopa to levodopa. SINEMET CR 50/200 contains carbidopa 50 mg/levodopa 200 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 should only be administrated as whole tablets. So that the controlled release properties of the products can be maintained, 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.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

INITIAL DOSAGE

Patients Who Have Not Received Prior Levodopa Therapy
When appropriate, levodopa therapy may be initiated with SINEMET CR 50/200. The initial recommended dose is 1 tablet of SINEMET CR 50/200 two or three times daily. Initial dosages should not exceed 600 mg per day of levodopa or be given at intervals of less than 6 hours.

Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations
Dosage with SINEMET CR 50/200 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). The interval between doses of SINEMET CR 50/200 should be 4-8 hours during the waking day. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

A guide for substitution of SINEMET CR 50/200 treatment for conventional levodopa/decarboxylase inhibitor combinations is shown in the table below:

Guidelines for Initial Conversion
from Levodopa/decarboxylase inhibitor to SINEMET CR 50/200

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

*For dosing ranges not shown in the table see DOSAGE and ADMINISTRATION, Initial Dosage - Patients currently treated with conventional levodopa/decarboxylase inhibitor combinations.

Patients Currently Treated With Levodopa Alone

Levodopa must be discontinued at least eight hours before therapy with SINEMET CR 50/200 is started. In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR 50/200 two or three times daily.

TITRATION

Following initiation of therapy, doses and dosing intervals may be increased or decreased, depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets of SINEMET CR 50/200 per day, administered as divided doses at intervals ranging from 4 to 12 hours during the waking day. Higher doses (up to 12 tablets) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR 50/200 are given at intervals of less than 4 hours, or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day. In some patients the onset of effect of the first morning dose may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET.

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

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 and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added to an existing treatment regimen for SINEMET CR.

A dose of SINEMET 25/100 can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

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.

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 DRUG INTERACTIONS, Other Drugs).

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

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.

PRECAUTIONS

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least 8 hours before therapy with SINEMET CR is started (at least 12 hours if slow-release plain levodopa has been administered).
Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. Dosage reduction may be required. 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.

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or a history of peptic ulcer disease or of convulsions.

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

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

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 carbidopa-levodopa combinations is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Levodopa has been associated with somnolence and episodes of sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients should be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines.

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

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy.

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).

Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioral symptoms of impulse control disorders (such as pathological gambling, hypersexuality, increased libido, compulsive spending/buying, and binge/compulsive eating) have been reported in patients treated with dopamine agonists and/or other dopaminergic treatments for Parkinson's disease. Review of treatment is recommended if such symptoms develop.

PREGNANCY

Although the effects of SINEMET CR on human pregnancy are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see Teratology and Reproductive Studies). Therefore, use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

NURSING MOTHERS

It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in breast milk was reported. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue nursing or to discontinue the use of SINEMET CR, taking into account the importance of the drug to the mother.

USE IN CHILDREN

Safety and effectiveness of SINEMET CR in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

DRUG INTERACTIONS

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

Antihypertensive agents:

Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations 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.

Antidepressants:

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.

Iron:

Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulfate or ferrous gluconate.

Other drugs:

Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones and risperidone) and isoniazid 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.

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

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see CONTRAINDICATIONS).

SIDE EFFECTS

In controlled clinical trials in patients with moderate to severe motor fluctuations, SINEMET CR did not produce side effects which were unique to the controlled release formulation.

The side effect reported most frequently was dyskinesia (a form of abnormal involuntary movements). A somewhat greater incidence of dyskinesias was seen with SINEMET CR than with SINEMET due to the replacement of "off" time (which is reduced with SINEMET CR) by "on" time (which is sometimes accompanied by dyskinesias).

Other side effects that also were reported frequently (above 2%) were: nausea, hallucinations, confusion, dizziness, chorea and dry mouth.

Side effects occurring less frequently (1-2%) were: dream abnormalities, dystonia, somnolence including very rarely excessive daytime somnolence and sudden sleep onset episodes, insomnia, depression, asthenia, vomiting, and anorexia.

Other side effects reported in clinical trials or in post-marketing experience include:
Body as a whole: chest pain, syncope.
Cardiovascular: palpitation, orthostatic effects including hypotensive episodes.
Gastrointestinal: constipation, diarrhea, dyspepsia, gastrointestinal pain, dark saliva.
Hypersensitivity: angioedema, urticaria, pruritus.
Metabolic: weight loss.
Nervous System/Psychiatric: Neuroleptic malignant syndrome, (see PRECAUTIONS), agitation, anxiety, decreased mental acuity, paresthesia, disorientation, fatigue, headache, extrapyramidal and movement disorders, falling, gait abnormalities, muscle cramps, on-off phenomenon, psychotic episodes including delusions and paranoid ideation.
In post-marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating have been reported with dopamine agonists and/or other dopaminergic treatments, and rarely in patients treated with levodopa, including SINEMET CR (see PRECAUTIONS).
Respiratory: dyspnea.
Skin: flushing, alopecia, rash, dark sweat.
Special Senses: blurred vision.
Urogenital: dark urine.

OTHER SIDE EFFECTS THAT HAVE BEEN REPORTED WITH LEVODOPA OR LEVODOPA/CARBIDOPA COMBINATIONS AND MAY BE POTENTIAL SIDE EFFECTS WITH "SINEMET" CR are listed below:

Cardiovascular: cardiac irregularities, hypertension, phlebitis.
Gastrointestinal: bitter taste, sialorrhea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

Hematologic: leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.
Nervous System/Psychiatric: ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome, euphoria and dementia, depression with suicidal tendencies.
Skin: increased sweating.
Special Senses: diplopia, dilated pupils, oculogyric crises.
Urogenital: urinary retention, urinary incontinence, priapism.
Miscellaneous: Weight gain, edema, weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see CONTRAINDICATIONS), Henoch-Schonlein purpura.

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 creatinine, uric acid, alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, and Coombs' test.

Decreased hemoglobin and hematocrit; elevated serum glucose; and white blood cells, bacteria and blood in the urine have been reported.

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.

OVERDOSAGE

Management of acute overdosage with SINEMET CR 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.

AVAILABILITY

To be filled in locally.

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