Tablets

Sinemet®

(carbidopa and levodopa)

SINEMET® is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, for use in the treatment of Parkinson's disease and syndrome.

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 the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine.

SINEMET improves overall therapeutic response as compared to levodopa. SINEMET provides effective long-lasting levodopa plasma levels at doses that are approximately 80 percent lower than those needed with levodopa alone.

While pyridoxine hydrochloride (Vitamin B6) is known to accelerate the peripheral metabolism of levodopa to dopamine, carbidopa prevents this action.

INDICATIONS

SINEMET is indicated for the treatment of Parkinson's disease and syndrome. It is useful in relieving many of the symptoms of parkinsonism, particularly rigidity and bradykinesia. SINEMET frequently is helpful in the management of tremor, dysphagia, sialorrhea, and postural instability associated with Parkinson's disease and syndrome.

When therapeutic response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not evenly controlled throughout the day, substitution of SINEMET usually is effective in reducing fluctuations in response.

By reducing certain adverse reactions produced by levodopa alone, SINEMET permits more patients to obtain adequate relief of the symptoms of Parkinson's disease.

SINEMET is also indicated for patients with Parkinsonism who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

DOSAGE AND ADMINISTRATION

The optimum daily dosage of SINEMET must be determined by careful titration in each patient. SINEMET tablets are available in a 1:4 ratio of carbidopa to levodopa (SINEMET 25/100 and SINEMET 12.5/50) as well as a 1:10 ratio (SINEMET 25/250 and SINEMET 10/100). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage.

Each tablet of SINEMET is designed to divide in half with minimal pressure.

GENERAL CONSIDERATIONS:

Dosage should be titrated to individual patient needs and this may require adjusting both the individual dose and the frequency of administration.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Standard antiparkinson drugs, other than levodopa alone, may be continued while SINEMET is being administered, although their dosage may have to be adjusted.

USUAL INITIAL DOSE:

Dosage is best initiated with one tablet of SINEMET 25/100 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage equivalent of eight tablets of SINEMET 25/100 a day is reached.

SINEMET 12.5/50 or 10/100 may be used to facilitate dosage titration according to the needs of the individual patient.

If SINEMET 10/100 or SINEMET 12.5/50 is used, dosage may be initiated with one tablet three or four times a day. However, this may not provide the optimal amount of carbidopa needed by many patients. Dosage may be increased by one tablet every day or every other day until a total of eight tablets (two tablets four times a day) is reached.

For patients starting with SINEMET 25/250, the initial dose is one-half tablet taken once or twice daily. However, this may not provide the optimal amount of carbidopa needed by many patients. If necessary, add 1/2 tablet every day or every other day until optimal response is reached.

Response has been observed in one day, and sometimes after one dose. Fully effective doses usually are reached within seven days as compared to weeks or months with levodopa alone.

HOW TO TRANSFER PATIENTS FROM LEVODOPA:

Because both therapeutic and adverse responses occur more rapidly with SINEMET than when levodopa is given, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with SINEMET than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Levodopa should be discontinued at least 12 hours before SINEMET is started (24 hours for slow-release preparations of levodopa). A daily dosage of SINEMET should be chosen that will provide approximately 20% of the previous levodopa daily dosage.

Patients who are taking less than 1500 mg of levodopa a day should be started on one tablet of SINEMET 25/100 three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is one tablet of SINEMET 25/250 three or four times a day

MAINTENANCE:

Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided for optimal inhibition of extracerebral decarboxylation of levodopa. When a greater proportion of carbidopa is required, one tablet of SINEMET 25/100 or SINEMET 12.5/50 may be substituted for each tablet of SINEMET 10/100.

When more levodopa is required, SINEMET 25/250 should be substituted for SINEMET 25/100, SINEMET 10/100, or SINEMET 12.5/50. If necessary, the dosage of SINEMET 25/250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

MAXIMUM RECOMMENDED DOSE:

Eight tablets of SINEMET 25/250 per day (200 mg of carbidopa and 2 g of levodopa). This is about 3 mg/kg of carbidopa, and 30 mg/kg of levodopa in a patient weighing 70 kg.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with SINEMET. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET.

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

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

PRECAUTIONS

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

SINEMET may be given to patients already receiving levodopa alone; however, the levodopa alone must be discontinued at least 12 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 20 percent of the previous levodopa dosage (See DOSAGE AND ADMINISTRATION).

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 may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of SINEMET may cause a recurrence. 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.

Caution should be exercised with concomitant administration of psychoactive drugs and SINEMET (see DRUG INTERACTIONS).

SINEMET 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 (because of the possibility of upper gastrointestinal hemorrhage) or of convulsions.

As with levodopa, care should be exercised in administering SINEMET to patients with a history of 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, 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 SINEMET 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.

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

If general anesthesia is required, SINEMET may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

PREGNANCY: Although the effects of SINEMET 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 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 human 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, taking into account the importance of the drug to the mother.

USE IN CHILDREN: Safety and effectiveness of SINEMET 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:

Antihypertensive agents: Symptomatic postural hypotension has occurred when SINEMET is added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required.

Antidepressants: For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricylic antidepressants and SINEMET.

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 D2 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 should be observed carefully for loss of therapeutic response.

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

Since levodopa competes with certain amino acids the absorption of levodopa may be impaired in some patients on a high protein diet.

SIDE EFFECTS

Side effects that occur frequently in patients receiving SINEMET are those due to the central neuropharmacologic activity of dopamine. These reactions usually can be diminished by dosage reduction. The most common side effects are dyskinesias, including choreiform, dystonic, and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

Other side effects reported in clinical trials or in post-marketing experience include:

Body as a whole: syncope, chest pain, anorexia.

Cardiovascular: cardiac irregularities and/or palpitation, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

Gastrointestinal: vomiting, gastrointestinal bleeding, development of duodenal ulcer, diarrhea, dark saliva.

Hemotologic: leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura.

Nervous System/Psychiatric: neuroleptic malignant syndrome (see PRECAUTIONS), bradykinetic episodes (the "on-off" phenomenon), dizziness, somnolence, including very rarely excessive daytime somnolence and sudden sleep onset episodes, paresthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion, increased libido.

In post-marketing use, pathological (compulsive) gambling has been reported rarely in patients treated with levodopa and/or dopamine receptor agonists.

Respiratory: dyspnea.

Skin: alopecia, rash, dark sweat.

Urogenital: dark urine.

Rarely convulsions have occurred; however, a causal relationship with SINEMET has not been established.

LABORATORY TESTS

Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with SINEMET. These include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, creatinine, uric acid, and positive Coombs' test. Decreased hemoglobin, 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.

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

Gastrointestinal: dyspepsia, dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of tongue.

Metabolic: weight gain or loss, edema.

Nervous System/Psychiatric: asthenia, decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle cramps, trismus, activation of latent Horner's syndrome, insomnia, anxiety, euphoria, falling and gait abnormalities.

Skin: flushing, increased sweating.

Special Senses: diplopia, blurred vision, dilated pupils, oculogyric crises.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see CONTRAINDICATIONS).

OVERDOSAGE

Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

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

AVAILABILITY

Tablets in blister pack of 20's.

Each tablet contains 25 mg of carbidopa & 250 mg of levodopa.

Do not use after expiry date.

Keep Medicament out of reach of children.

STORAGE CONDITIONS

Store in a dry place below 30°C, protected from light.

Do not refrigerate.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold you the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

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