

Name of Medicine

SINEMET CR[®]

carbidopa/levodopa

50/200 mg tablet

Presentation

50/200 mg: A dappled peach coloured, oval shaped, biconvex tablet scored and engraved with MSD 521 on one side and SINEMET CR on the other. (Thickness 4 mm.)

Therapeutic Class

Antiparkinson agent.

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 characterised by end-of-dose deterioration ("wearing-off" phenomenon), peak dose dyskinesias, akinesia, or similar evidence of short-duration motor disturbances.

Dosage and 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 50/200 may be administered as whole or as half tablets. So that the controlled release properties of the product can be maintained, tablets should not be chewed or crushed.

Standard anti-Parkinson medicines, 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 B6).

Initial Dosage

Patients Who Have Not Received Prior Levodopa Therapy

In early stage patients who have not had prior levodopa therapy, the initial recommended dose is a half tablet of SINEMET CR 50/200 twice daily. When appropriate, levodopa therapy may also be initiated with SINEMET CR 50/200 1 tablet 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 Actions, *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 1/2 tab b.i.d.or 1 tab t.i.d.
700 - 800	A total of 4 tabs in 3 or more divided doses (e.g. 1 1/2 tab a.m., 1 1/2 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.

Patients currently treated with conventional levodopa/decarboxylase inhibitor combinations.

Half a tablet of SINEMET CR 50/200 can be used to facilitate titration when 100 mg steps are required.

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 (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 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 Warnings and Precautions).

If general anaesthesia 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 Interactions, *Other Medicines*).

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.

Warnings and 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 therapy-induced extrapyramidal reactions.

Periodic evaluations of hepatic, haematopoietic, 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).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease. Health care professionals should inform their patients to seek help from their doctor if they, their family or their carer notice that their behaviour is unusual.

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 medicine 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 medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing 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 medicine 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.

Animal Toxicology

The average daily doses of carbidopa and levodopa used concomitantly in humans are 100 mg and 1 g respectively, which is approximately 2 mg/kg of carbidopa and 20 mg/kg levodopa.

Oral LD₅₀s of carbidopa are 1750 mg/kg in adult female mice, and 4810 and 5610 mg/kg in young adult female and male rats, respectively. The acute oral toxicity of carbidopa is similar in weanling and adult rats, but the compound is more toxic in infant rats. Signs of therapy effect were similar in both mice and rats, and consisted of ptosis, ataxia, and decreased activity. Bradypnea occurred in the mice. Deaths usually took place overnight, with occasional deaths up to 12 days.

Oral LD₅₀s of levodopa range from 800 mg/kg in infant male and female rats to 2260 mg/kg in young adult female rats. Signs of therapy effect were vocalisation, irritability, excitability, ataxia, and increased activity followed in one to two hours by decreased activity. Deaths usually occurred in 30 minutes to overnight, with occasional deaths up to five days.

Oral LD₅₀s of various combinations of carbidopa and levodopa in mice range from 1930 mg/kg for a 1:1 ratio to 3270 mg/kg for a 1:3 ratio. These amounts are the sum of the individual doses of carbidopa and levodopa. Ratios tested above 1:3 (1:4, 1:5, 1:10) did not appreciably change the LD₅₀ value from that found for the 1:3 ratio. The ratios of 1:3 and above were less toxic than the 1:1 and 1:2 ratios. Signs of toxicity included erect tails, piloerection, ataxia, lacrimation, and increased activity. Clonic convulsions and increased irritability were seen at doses of 1500 mg/kg and higher. Coarse head and body tremors were seen at doses of 4120 mg/kg and higher. Deaths occurred in 30 minutes to 24 hours with doses of 4120 and 5780 mg/kg, and up to 12 days after dosage with 2940 mg/kg.

Chronic oral toxicity studies of carbidopa have been conducted for one year in monkeys and 96 weeks in rats, using doses from 25 to 135 mg/kg/day. No treatment-related effects were observed in monkeys. In rats, flaccidity occurred in some animals in all dosage groups. Mean kidney weights of rats in the highest dosage group were significantly higher than those of corresponding controls, although no gross or microscopic alterations were observed to account for this. There were no histologic changes due to treatment. Carbidopa did not influence the type or incidence of neoplasia in the 96-week study in rats.

Carbidopa given to dogs resulted in pyridoxine deficiency which was prevented by coadministration of pyridoxine.

Except for pyridoxine deficiency in dogs, carbidopa has not exhibited toxicity patterns associated with hydrazines.

Three dosage ratios of carbidopa and levodopa given orally to monkeys for 54 weeks and

rats for 106 weeks showed that the principal physical effects were due to the pharmacologic activity of the compounds. The dosages studied were (carbidopa/levodopa) 10/20, 10/50, and 10/100 mg/kg/day. Dosages of 10/20 mg/kg/day had no apparent physical effects.

Hyperactivity occurred in monkeys at dosages of 10/50 and 10/100 mg/kg/day, and continued for 32 weeks with the higher dose. With the 10/50 mg/kg/day dose, hyperactivity decreased as the study progressed and was not observed after the fourteenth week. Muscular incoordination and weakness were observed until the twenty-second week with the 10/100 mg/kg/day dose. Pathologic studies did not show any morphologic changes.

Rats that received 10/50 and 10/100 mg/kg/day had a decrease in normal activity and displayed abnormal body positions. The higher dose caused excessive salivation. There was a decrease in body weight gain. Pathologic studies disclosed very slight hypertrophy of the acinar cells of the submaxillary glands of two rats which had received 10/100 mg/kg/day for 26 weeks. No histomorphologic effects were found with any dose after 54 or 106 weeks. Hypertrophy of the acinar cells of the salivary gland has been noted in rats treated with higher doses of the combination for shorter periods of time and with levodopa alone.

Teratology and Reproductive Studies

Carbidopa showed no evidence of teratogenicity in mice or rabbits at doses of 120 mg/kg/day.

Levodopa produced visceral and skeletal malformations in rabbits at doses of 125 and 250 mg/kg/day.

With combinations of carbidopa and levodopa, in doses ranging from 25/250 to 100/500 mg/kg/day, there was no evidence of teratogenicity in mice, but in rabbits visceral and skeletal malformations occurred which were quantitatively and qualitatively similar to those seen with levodopa alone.

Carbidopa had no effect on the mating performance, fertility or survival of the young when administered orally to rats at doses of 30, 60, or 120 mg/kg/day. The highest dose caused a moderate decrease in body weight gain in males.

The administration of carbidopa/levodopa at dose levels of 10/20, 10/50 or 10/100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the growth and survival of their young.

Carcinogenesis

There were no significant differences between treated and control rats with respect to mortality or neoplasia in a 96 week study of carbidopa at oral doses of 25, 45 or 135 mg/kg/day.

Combinations of carbidopa and levodopa (10/20, 10/50 and 10/100 mg/kg/day) were given orally to rats for 106 weeks. No effect on mortality or incidence and type of neoplasia was seen when compared to concurrent controls.

Adverse Effects

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

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

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

Other adverse effects reported in clinical trials or in post-marketing experience included:
Body as a whole: chest pain, syncope.

Cardiovascular: palpitation, orthostatic effects including hypotensive episodes.

Gastrointestinal: constipation, diarrhoea, dyspepsia, gastrointestinal pain, dark saliva.

Hypersensitivity: angioedema, urticaria, pruritus.

Metabolic: weight loss.

Nervous System/Psychiatric: Neuroleptic malignant syndrome, (see Warnings and 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.

Patients treated with dopamine agonists for the treatment of Parkinson's Disease, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality. These effects are generally reversible upon reduction of the dose or treatment discontinuation.

Respiratory: dyspnoea.

Skin: flushing, alopecia, rash, dark sweat.

Special Senses: blurred vision.

Urogenital: dark urine.

Other adverse effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential adverse effects with SINEMET CR are listed below:

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.

Gastrointestinal: bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

Cardiovascular: cardiac irregularities, hypertension, phlebitis.

Skin: increased sweating.

Urogenital: urinary retention, urinary incontinence.

Special Senses: diplopia, dilated pupils, oculogyric crises.

Haematologic: leukopaenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

Miscellaneous: weight gain, oedema, weakness, faintness, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see Contraindications), Henoch-Schönlein 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 alkaline phosphatase, SGOT (ALT), SGPT (AST), lactic dehydrogenase, bilirubin, blood urea nitrogen, and Coombs' test.

Decreased haemoglobin, haematocrit, 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.

Interactions

Caution should be exercised when the following medicines 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 medicines. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive agent may be required.

Antidepressants

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-A-inhibitors, see Contraindications.)

Iron

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

Other medicines

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 agents with SINEMET CR 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).

Additional Information on Interactions

Although specific interaction studies were not performed with other concomitant agents, in clinical trials of SINEMET CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, beta blockers, thiazides, angiotensin converting enzyme inhibitors, calcium channel blockers, digitalis preparations, H₂ antagonists, salicylates and other nonsteroidal anti-inflammatory medicines. SINEMET CR was also used with other antiparkinson agents (see Dosage and Administration).

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 agents 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.

Actions

SINEMET CR is a combination of carbidopa, MSD, an aromatic amino acid decarboxylase inhibitor, and levodopa, MSD, 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 characterised by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ("on-off" phenomenon) is characterised 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 adverse effects, especially those which are attributable to dopamine being formed in extracerebral tissues.

SINEMET CR is designed to release its 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.

Pharmacokinetics

The pharmacokinetics of levodopa following administration of SINEMET CR 50/200 were studied in young and elderly healthy volunteers. The mean time to peak plasma levodopa level after SINEMET CR 50/200 was approximately two hours compared to 0.75 hours with SINEMET. The mean peak plasma levodopa levels were 60 percent lower with SINEMET CR 50/200 than with SINEMET. The in vivo absorption of levodopa following administration of SINEMET CR 50/200 was continuous for 4 to 6 hours. In these studies, as with patients, plasma levodopa concentrations fluctuated in a narrower range than with SINEMET. Because the bioavailability of levodopa from SINEMET CR 50/200, relative to SINEMET, is approximately 70 percent, the daily dosage of levodopa in the controlled-release formulation will usually be higher than with conventional formulations. There was no evidence that SINEMET CR 50/200 released its ingredients in a rapid or uncontrolled fashion.

Pharmaceutical Precautions

Store below 30°C. Store in a tightly closed container.

Medicine Classification

Prescription Medicine.

Package Quantities

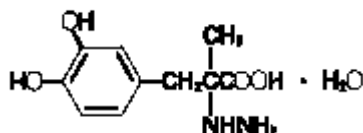
SINEMET CR 50/200 is available in bottles of 100 tablets.

Further Information

Chemistry and Pharmacology

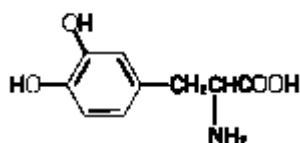
SINEMET CR is a controlled-release formulation of carbidopa, MSD, and levodopa, MSD, in a ratio of 1:4. The tablet contains a polymer-based medicine delivery system which controls the release of carbidopa and levodopa as it slowly erodes. Excipients include magnesium stearate, red ferric oxide and quinoline yellow (E104) aluminium lake.

Carbidopa, MSD, an inhibitor of aromatic amino acid decarboxylase, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L- alpha-hydrazino-alpha-methyl-beta-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$ and its structural formula is:



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

Levodopa, MSD, 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-alpha-amino-beta-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_9NO_4$ and its structural formula is:



Symptoms of Parkinson's disease have been related to depletion of dopamine in the corpus striatum of the brain. Levodopa, the metabolic precursor of dopamine, relieves the symptoms of Parkinson's disease presumably by being converted to dopamine in the brain. Following oral administration, levodopa is decarboxylated rapidly and converted to dopamine in extracerebral tissues, and only a small amount of unchanged levodopa reaches the central nervous system.

Thus, large doses of levodopa are required at frequent intervals for adequate therapeutic effect, and often are attended by many adverse reactions, some of which are attributable to dopamine being formed in extracerebral tissue.

Carbidopa, which does not cross the blood-brain barrier, inhibits only extracerebral decarboxylation of levodopa, principally in the intestinal mucosa, making more levodopa available for transport to the brain and conversion to dopamine.

In dogs, reduced formation of dopamine in extracerebral tissues, such as the heart, provides protection against the development of dopamine-induced cardiac arrhythmias. Clinical studies tend to support the hypothesis of a similar protective effect in humans although controlled data are too limited at the present time to draw firm conclusions.

Following coadministration of carbidopa and levodopa in humans, plasma levels of levodopa were increased markedly over those found when the same dosage of levodopa was given alone, while plasma levels of dopamine and homovanillic acid, two principal metabolites of levodopa, were reduced markedly.

Pyridoxine hydrochloride (vitamin B₆), in oral doses of 10 mg to 25 mg, has been noted to reverse rapidly the antiparkinsonian effects of levodopa. Carbidopa prevents this action of pyridoxine. In a study in which patients received 100 to 500 mg of pyridoxine a day while being treated with carbidopa and levodopa in combination, there was no reversal of therapeutic effect.

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