**NAME AND STRENGTH OF ACTIVE INGREDIENTS**

LEVODOPA + CARBIDOPA (SINEMET) is available for oral administration as tablets containing 100 mg levodopa and 25 mg carbidopa (LEVODOPA + CARBIDOPA (SINEMET) 100/25) as well as a 10:1 ratio, each tablet containing 250 mg levodopa and 25 mg carbidopa (LEVODOPA + CARBIDOPA (SINEMET) 250/25).

**PRODUCT DESCRIPTION**

LEVODOPA + CARBIDOPA (SINEMET) is a combination of carbidopa, MSD, 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.

LEVODOPA + CARBIDOPA (SINEMET) improves over all therapeutic response as compared to levodopa. LEVODOPA + CARBIDOPA (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.

Carbidopa, 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 \((-\)-\(\alpha\)-hydrazino-\(\alpha\)-methyl-\(\beta\)-(3,4-dihydroxy-benzene) propanoic acid monohydrate. The empirical formula is \(\text{C}_{10}\text{H}_{14}\text{N}_{2}\text{O}_{4}\cdot\text{H}_{2}\text{O}\) and the structural formula is:

![Chemical structure of carbidopa](image)

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 \((-\)-\(\alpha\)-amino-\(\beta\)-(3,4-dihydroxybenzene) propanoic acid. The empirical formula is \(\text{C}_{9}\text{H}_{11}\text{NO}_{4}\) and the 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 are often 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 extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and conversion to dopamine.

Since the decarboxylase inhibiting activity of carbidopa is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. 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 man, 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.

**PHARMACOKINETICS**

**ONSET OF ACTION WITH USUAL DOSES**

Response has been observed in one day and sometimes after one dose. Fully effective doses usually are reached within seven days.

The carbidopa component of LEVODOPA + CARBIDOPA (SINEMET) 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 CNS effects, e.g., dyskinesias, may occur at lower dosages and sooner during therapy with LEVODOPA + CARBIDOPA (SINEMET) than with levodopa.

**HALF-LIFE**

The plasma half-life of levodopa is about 50 minutes. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1 1/2 hours.

**METABOLISM OF CARBIDOPA**

Following an oral dose of radioactive labeled carbidopa to healthy subjects and to patients with Parkinson's disease, maximum plasma levels of radioactivity were reached in two to four hours in the
normal subjects and in one and one-half to five hours in the patients. Approximately equal quantities were excreted in the urine and the feces by both groups.

Comparison of urinary metabolites in healthy subjects and patients indicated that the drug is metabolized to the same degree in both. Urinary excretion of unchanged drug was essentially complete in seven hours and represented 35 percent of the total urinary radioactivity. Only metabolites were present thereafter. No hydrazines were found.

Among the metabolites excreted by man are $\alpha$-methyl-3-methoxy-4-hydroxyphenylpropionic acid and $\alpha$-methyl-3,4 dihydroxyphenylpropionic acid. These accounted for approximately 14 and 10 percent, respectively, of the radioactive metabolites excreted. Two minor metabolites were found. One was identified as 3,4 dihydroxyphenyl acetone and the other tentatively identified as N-methyl-carbidopa. They each accounted for less than five percent of the urinary metabolites. Unchanged carbidopa also is present in the urine. No conjugates were found.

**METABOLISM OF LEVODOPA**

Levodopa is absorbed rapidly from the gastrointestinal tract and extensively metabolized. Although more than 30 metabolites may be formed, it is converted mainly to dopamine, epinephrine and norepinephrine, and eventually to dihydroxyphenylacetic acid, homovanillic acid, and vanilmandelic acid. 3-O-methyldopa appears in the plasma and cerebrospinal fluid. Its significance is not known.

When single test doses of radioactive levodopa are given to fasting patients with Parkinson's disease, plasma levels of radioactivity reach a peak level in one-half to two hours and remain measurable for four to six hours. At peak levels, about 30% of radioactivity appears as catecholamines, 15% as dopamine, and 10% as dopa. Radioactive compounds are excreted rapidly in the urine, one-third of the dose appearing in two hours. Eighty to ninety percent of urinary metabolites are phenylcarboxylic acids, principally homovanillic acid. Over 24 hours, one to two percent of recovered radioactivity is dopamine, and less than one percent is epinephrine, norepinephrine, and unchanged levodopa.

**EFFECT OF CARBIDOPA ON LEVODOPA METABOLISM**

In healthy subjects, carbidopa increased plasma levels of levodopa by statistically significant amounts, as measured against placebo. This has been demonstrated when carbidopa was given before levodopa and when the two drugs were given simultaneously. In one study, pretreatment with carbidopa increased plasma levels of a single dose of levodopa about five times and extended the duration of measurable plasma concentrations of levodopa from four hours to eight hours. When the two drugs were given simultaneously in other studies, similar results were obtained.

In a study in which a single dose of stem-labeled levodopa was given to patients with Parkinson's disease who had been pretreated with carbidopa, there was an increase in the half-life of total plasma radioactivity derived from the levodopa, from 3 hours to 15 hours. The proportion of radioactivity remaining as unmetabolized levodopa was increased at least three times by carbidopa. Plasma and urinary dopamine and homovanillic acid were both decreased by carbidopa pretreatment.

**INDICATIONS**

LEVODOPA + CARBIDOPA (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. LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) usually is effective in reducing fluctuations in response.

By reducing certain adverse reactions produced by levodopa alone, LEVODOPA + CARBIDOPA (SINEMET) permits more patients to obtain adequate relief of the symptoms of Parkinson's disease.
LEVODOPA + CARBIDOPA (SINEMET) is also indicated for patients with Parkinsonism who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B₆).

**RECOMMENDED DOSE**

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

Each tablet of LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) is being administered, although their dosage may have to be adjusted.

**USUAL INITIAL DOSAGE**

Dosage is best initiated with one tablet of LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) 25/100 a day is reached.

For patients starting with LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) than when levodopa is given, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) is started (24 hours for slow-release preparations of levodopa). A daily dosage of LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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 more levodopa is required, LEVODOPA + CARBIDOPA (SINEMET) 25/250 should be substituted for LEVODOPA + CARBIDOPA (SINEMET) 25/100. If necessary, the dosage of LEVODOPA + CARBIDOPA (SINEMET) 25/250 may be increased by one-half or one tablet everyday 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 LEVODOPA + CARBIDOPA (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.

MODE OF ADMINISTRATION

LEVODOPA + CARBIDOPA (SINEMET) is available for oral administration as tablets.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with LEVODOPA + CARBIDOPA (SINEMET). These inhibitors must be discontinued at least two weeks prior to initiating therapy with LEVODOPA + CARBIDOPA (SINEMET). LEVODOPA + CARBIDOPA (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 INTERACTIONS WITH OTHER MEDICAMENTS, Other Drugs).

LEVODOPA + CARBIDOPA (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, LEVODOPA + CARBIDOPA (SINEMET) should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

WARNINGS AND PRECAUTIONS

LEVODOPA + CARBIDOPA (SINEMET) is not recommended for the treatment of drug-induced extrapyramidal reactions.

LEVODOPA + CARBIDOPA (SINEMET) may be given to patients already receiving levodopa alone; however, the levodopa alone must be discontinued at least 12 hours before LEVODOPA + CARBIDOPA (SINEMET) is started. LEVODOPA + CARBIDOPA (SINEMET) should be substituted at a dosage that will provide approximately 20 percent of the previous levodopa dosage (see RECOMMENDED DOSE).

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, LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) (see INTERACTIONS WITH OTHER MEDICAMENTS).

LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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, LEVODOPA + CARBIDOPA (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.

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 LEVODOPA + CARBIDOPA (SINEMET) for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Pathological gambling, hypersexuality, and increased libido have been reported in patients treated with dopamine agonists for Parkinson's disease.

### INTERACTIONS WITH OTHER MEDICAMENTS

Caution should be exercised when the following drugs are administered concomitantly with LEVODOPA + CARBIDOPA (SINEMET):

**Antihypertensive agents:**
Symptomatic postural hypotension has occurred when LEVODOPA + CARBIDOPA (SINEMET) is added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with LEVODOPA + CARBIDOPA (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 tricyclic antidepressants and LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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.

**PREGNANCY AND LACTATION**

Although the effects of LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

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 LEVODOPA + CARBIDOPA (SINEMET), taking into account the importance of the drug to the mother.

**USE IN CHILDREN**

Safety and effectiveness of LEVODOPA + CARBIDOPA (SINEMET) in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

**UNDESIRABLE EFFECTS**

Side effects that occur frequently in patients receiving LEVODOPA + CARBIDOPA (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.

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

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

Nervous System/Psychiatric: neuroleptic malignant syndrome (see WARNINGS AND 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 LEVODOPA + CARBIDOPA (SINEMET) has not been established.

LABORATORY TESTS

Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (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).

**OVERDOSE AND TREATMENT**

Management of acute overdosage with LEVODOPA + CARBIDOPA (SINEMET) is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of LEVODOPA + CARBIDOPA (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 LEVODOPA + CARBIDOPA (SINEMET) should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

**STORAGE CONDITION**

Store at temperatures not exceeding 30°C.

**DOSAGE FORMS AND PACKAGING AVAILABLE**

LEVODOPA + CARBIDOPA (SINEMET) Tablets are available in a 4:1 ratio, each tablet containing 100 mg levodopa and 25 mg carbidopa (LEVODOPA + CARBIDOPA (SINEMET) 100/25) as well as a 10:1 ratio, each tablet containing 250 mg levodopa and 25 mg carbidopa (LEVODOPA + CARBIDOPA (SINEMET) 250/25). Both dosage strengths are supplied in amber glass bottles of 100 tablets.

**CAUTION**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without the prescription of a physician.

**DATE OF REVISION OF PACKAGE INSERT**

PHL-SEM-T-072009