

# **ATTACHMENT 2**

PDR® entry for

SINEMET® (DuPont)

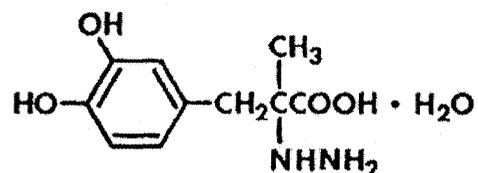
(CARBIDOPA-LEVODOPA)

TABLETS

## DESCRIPTION

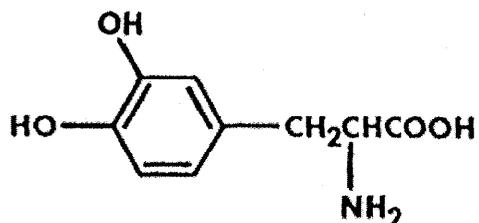
SINEMET (Carbidopa-Levodopa) is a combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-(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 anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-(alpha)-amino-(beta)-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is  $C_9H_{11}NO_4$ , and its structural formula is:



SINEMET is supplied as tablets in three strengths:

SINEMET 25-100, containing 25 mg of carbidopa and 100 mg of levodopa.

SINEMET 10-100, containing 10 mg of carbidopa and 100 mg of levodopa.

SINEMET 25-250, containing 25 mg of carbidopa and 250 mg of levodopa.

Inactive ingredients are cellulose, magnesium stearate, and starch. Tablets SINEMET 10-100 and 25-250 also contain FD&C Blue 2. Tablets SINEMET 25-100 also contain D&C Yellow 10 and FD&C Yellow 6.

## CLINICAL PHARMACOLOGY

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

### *Mechanism of Action*

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

### *Pharmacodynamics*

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

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

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients, this reduction in nausea and vomiting will permit more rapid dosage titration.

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

### *Pharmacokinetics*

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

The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours. At steady state, the bioavailability of carbidopa from SINEMET tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa produced greater urinary excretion of levodopa in proportion to the excretion of dopamine than administration of the two drugs at separate times.

Pyridoxine hydrochloride (vitamin B<sub>6</sub>), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B<sub>6</sub>).

## INDICATIONS AND USAGE

SINEMET is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication. SINEMET is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B<sub>6</sub>).

In some patients a somewhat smoother antiparkinsonian effect results from therapy with SINEMET than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from SINEMET.

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa.

Certain patients who responded poorly to levodopa have improved when SINEMET was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give SINEMET to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing SINEMET with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

## 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 PRECAUTIONS, Drug Interactions).

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

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

## WARNINGS

**When SINEMET (Carbidopa-Levodopa) is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least twelve hours before therapy with SINEMET (Carbidopa-Levodopa) is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See DOSAGE AND ADMINISTRATION section before initiating therapy.**

The addition of carbidopa with levodopa in the form of SINEMET reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa permits more levodopa to reach the brain and more dopamine to be formed, certain adverse CNS effects, e.g., dyskinesias (involuntary movements), may occur at lower dosages and sooner with SINEMET than with levodopa alone.

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

As with levodopa, SINEMET may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. 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 should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

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

**Neuroleptic Malignant Syndrome (NMS):** Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reduction or withdrawal of therapy with SINEMET. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

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

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

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

## PRECAUTIONS

### *General*

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

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

### *Information for Patients*

The patient should be informed that SINEMET is an immediate-release formulation of carbidopa-levodopa that is designed to begin release of ingredients within 30 minutes. It is important that SINEMET be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a 'wearing-off' effect may occur at the end of the dosing interval. The physician should be notified if such response poses a problem to life-style.

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

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

NOTE: The suggested advice to patients being treated with SINEMET is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

### *Laboratory Tests*

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

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

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

### *Drug Interactions*

Caution should be exercised when the following drugs are administered concomitantly with SINEMET (Carbidopa-Levodopa).

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

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

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

Dopamine D<sub>2</sub> receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Iron salts may reduce the bioavailability of levodopa and carbidopa. The clinical relevance is unclear.

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

#### *Carcinogenesis, Mutagenesis, Impairment of Fertility*

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

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

#### *Pregnancy*

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

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

#### *Nursing Mothers*

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET is administered to a nursing woman.

#### *Pediatric Use*

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

## **ADVERSE REACTIONS**

The most common adverse reactions reported with SINEMET have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea.

The following other adverse reactions have been reported with SINEMET:

*Body as a Whole:* chest pain, asthenia.

*Cardiovascular:* cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

*Gastrointestinal:* dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

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

*Hypersensitivity:* angioedema, urticaria, pruritus, Henoch-Schonlein purpura, bullous lesions (including pemphigus-like reactions).

*Musculoskeletal:* back pain, shoulder pain, muscle cramps.

*Nervous System/Psychiatric:* psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (see WARNINGS), bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, increased libido. Convulsions also have occurred; however, a casual relationship with SINEMET has not been established.

*Respiratory:* dyspnea, upper respiratory infection.

*Skin:* rash, increased sweating, alopecia, dark sweat.

*Urogenital:* urinary tract infection, urinary frequency, dark urine.

*Laboratory Tests:* decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

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

*Body as a Whole:* abdominal pain and distress, fatigue.

*Cardiovascular:* myocardial infarction.

*Gastrointestinal:* gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

*Metabolic:* edema, weight gain, weight loss.

*Musculoskeletal:* leg pain.

*Nervous System/Psychiatric:* ataxia, extrapyramidal disorder, falling, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

*Respiratory:* pharyngeal pain, cough.

*Skin:* malignant melanoma (see also CONTRAINDICATIONS), flushing.

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

*Urogenital:* urinary retention, urinary incontinence, priapism.

*Miscellaneous:* bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

*Laboratory Tests:* decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

## OVERDOSAGE

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

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate anti-arrhythmic 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.

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

## DOSAGE AND ADMINISTRATION

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) as well as 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.

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.

### *Usual Initial Dosage*

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 of eight tablets of SINEMET 25-100 a day is reached.

If SINEMET 10-100 is used, dosage may be initiated with one tablet three or four times a day. However, this will not provide an adequate amount of carbidopa for many patients. Dosage may be increased by one tablet every day or every other day until a total of eight tablets (2 tablets q.i.d.) is reached.

### *How to Transfer Patients from Levodopa*

**Levodopa must be discontinued at least twelve hours before starting SINEMET (Carbidopa-Levodopa).** A daily dosage of SINEMET should be chosen that will provide approximately 25 percent of the previous levodopa 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. When a greater proportion of carbidopa is required, one tablet of SINEMET 25-100 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 or SINEMET 10-100. 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.

Because both therapeutic and adverse responses occur more rapidly with SINEMET than with levodopa alone, 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.

#### *Addition of Other Antiparkinsonian Medications*

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET is being administered, although dosage adjustments may be required.

#### *Interruption of Therapy*

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of SINEMET. Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET is required, especially if the patient is receiving neuroleptics. (See **WARNINGS**.) 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 patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

### **HOW SUPPLIED**

Tablets SINEMET 25-100 are yellow, oval, uncoated tablets, that are scored and coded 650 on one side and SINEMET on the other side. They are supplied as follows:

**NDC 0056-0650-68** bottles of 100

**NDC 0056-0650-28** unit dose packages of 100.

Tablets SINEMET 10-100 are dark dapple-blue, oval, uncoated tablets, that are scored and coded 647 on one side and SINEMET on the other side. They are supplied as follows:

**NDC 0056-0647-68** bottles of 100

**NDC 0056-0647-28** unit dose packages of 100.

Tablets SINEMET 25-250 are light dapple-blue, oval, uncoated tablets, that are scored and coded 654 on one side and SINEMET on the other side. They are supplied as follows:

**NDC 0056-0654-68** bottles of 100

**NDC 0056-0654-28** unit dose packages of 100.

### **Storage**

Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

Manufactured by:

**MERCK & CO., INC.**

WEST POINT, PA 19486, USA

For:

### **DuPont Pharma**

Wilmington, Delaware 19880

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