

PRODUCT MONOGRAPH

 **SINEMET[®]**

levodopa and carbidopa tablets, USP

100 mg/25 mg
100 mg levodopa and 25 mg carbidopa

250 mg/25 mg
250 mg levodopa and 25 mg carbidopa

Antiparkinson Agent

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levodopa and carbidopa tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Non-Medicinal Ingredients |
|-------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------|
| oral | tablet 100 mg/25 mg, 250 mg/25 mg | Pregelatinized starch For a complete listing, see <i>DOSAGE FORMS, COMPOSITION AND PACKAGING</i> section. |

INDICATIONS AND CLINICAL USE

SINEMET[®] (levodopa and carbidopa) is indicated for the treatment of Parkinson's disease.

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

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

Pediatrics (< 18 years of age):

The safety and effectiveness of SINEMET[®] in patients under 18 years of age has not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with SINEMET[®] (levodopa and carbidopa). These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET[®]. SINEMET[®] may be administered concomitantly with a MAO inhibitor with selectivity for MAO type B (e.g. selegiline HCl) (see DRUG INTERACTIONS, Drug-Drug Interactions, Psychoactive Drugs) at the manufacturer's recommended dose which maintains selectivity for MAO type B.

- SINEMET[®] should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.
- As with levodopa, SINEMET[®] should not be given when administration of a sympathomimetic amine is contraindicated (e.g., epinephrine, norepinephrine or isoproterenol).
- 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 AND PRECAUTIONS

Serious Warnings and Precautions

Sudden Onset of Sleep

Patients receiving treatment with SINEMET[®] (levodopa and carbidopa) and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including the driving of a car, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on SINEMET[®], others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs and should be specifically asked about factors that may increase the risk with SINEMET[®] such as concomitant medications or the presence of sleep disorders. Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking SINEMET[®]. If drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician.

Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products.

While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Currently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness.

General

When patients already receiving levodopa are switched to SINEMET[®], levodopa must be discontinued for at least 12 hours or more before SINEMET[®] is started. SINEMET[®] should be substituted at a dosage that will provide approximately 20% of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Patients who are taking SINEMET[®] should be instructed not to take additional levodopa unless it is prescribed by the physician.

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy with SINEMET[®] (levodopa and carbidopa).

Physical Activity

Patients who improve while on therapy with SINEMET[®] should increase physical activities gradually, with caution, consistent with other medical considerations such as the presence of osteoporosis or phlebothrombosis.

Cardiovascular

Care should be exercised in administering SINEMET[®] to patients with a history of myocardial infarction or who have 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.

Gastrointestinal

SINEMET[®] should be administered cautiously to patients with a history of peptic ulcer disease due to the possibility of upper gastrointestinal hemorrhage.

Neurologic

The levodopa induced involuntary movements and ‘on and off’ phenomenon may appear earlier with combination therapy.

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. Because carbidopa permits more levodopa to reach the brain and thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with SINEMET[®] than with levodopa. The occurrence of dyskinesias may require dosage reduction.

SINEMET[®] should be used cautiously in patients who have a history of seizures or have conditions associated with seizure or have a lowered seizure threshold.

Neuroleptic Malignant Syndrome: A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, altered consciousness, mental changes, autonomic instability and increased serum creatine phosphokinase has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. Therefore, patients should be observed carefully when the dosage of SINEMET[®] is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Psychomotor Performance

Certain side effects that have been reported with SINEMET[®] may affect some patients' ability to drive or operate machinery.

Given the reported cases of somnolence and sudden onset of sleep (not necessarily preceded by somnolence), physicians should caution patients about the risk of operating hazardous machinery, including driving motor vehicles, while taking SINEMET[®]. If drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Sudden Onset of Sleep).

Ophthalmologic

Use in Patients with Glaucoma: Pupillary dilatation and activation of latent Horner's syndrome have been reported during levodopa treatment. Patients with chronic wide angle glaucoma should therefore be treated cautiously with SINEMET[®]. The intraocular pressure should be well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Peri-Operative Considerations

If general anesthesia is required, therapy with 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 (see DOSAGE AND ADMINISTRATION, Adjustment and Maintenance of Therapy).

Psychiatric

Patients should be monitored carefully for the development of depression with suicidal tendencies. Patients with past or current psychoses should be treated with caution.

Behavioural Changes

Patients and caregivers should be advised to adhere to dosage instructions given by the physician. Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioral symptoms of impulse control disorders, including pathological (compulsive) gambling, hypersexuality, increased libido, compulsive spending/buying, and binge/compulsive eating, have been reported in patients treated with dopaminergic agonists and/or other dopaminergic treatments for Parkinson's disease, including SINEMET[®] (see ADVERSE REACTIONS). Literature and postmarketing reports have described a very rare addictive pattern of dopamine replacement therapy, in which patients use doses in excess of those required to control their motor symptoms. Review of treatment is recommended if such symptoms develop.

Hallucinations

Hallucinations and confusion are known side effects of treatment with dopaminergic agents, including levodopa. Patients should be aware of the fact that hallucinations (mostly visual) can occur.

Skin

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 healthcare providers are advised to monitor for melanomas frequently and on a regular basis when using SINEMET[®] for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Special Populations

Pregnant Women: Although the effects of SINEMET[®] on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see TOXICOLOGY, Teratologic and Reproductive Studies). Therefore, use of SINEMET[®] in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to the mother and to the fetus.

Nursing Women: 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. SINEMET[®] should not be given to nursing mothers unless the anticipated benefits to the mother outweigh the potential hazards to the infant.

Pediatrics (< 18 years of age): The safety of SINEMET[®] in patients under 18 years of age has not been established.

Monitoring and Laboratory Tests

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy with SINEMET[®] (levodopa and carbidopa).

SINEMET[®] may cause a false-positive reaction for urinary ketone bodies when a tape test is used for determination of ketonuria. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or levodopa-carbidopa therapy (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

ADVERSE REACTIONS

Clinical Trial and Post-Market Adverse Drug Reactions

The most common serious adverse reactions occurring with SINEMET[®] (levodopa and carbidopa) are dyskinesias, including choreiform, dystonic and other involuntary movements, and nausea. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET[®] has not been established.

Other adverse reactions reported in clinical trials or in post-marketing experience include:

Body as a whole:

Syncope, chest pain, anorexia, asthenia.

Cardiovascular:

Cardiac irregularities and/or palpitation, hypotension, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

Gastrointestinal:

Vomiting, gastrointestinal bleeding, development of duodenal ulcer, diarrhea, dark saliva, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic:

Leukopenia, hemolytic and non-hemolytic anemia, thrombocytopenia, agranulocytosis.

Hypersensitivity:

Angioedema, urticaria, pruritus, Henoch-Schönlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal:

Back pain, shoulder pain, muscle cramps.

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, dream abnormalities including nightmares, insomnia, headache, depression with or without development of suicidal tendencies, dementia, agitation, confusion.

In post-marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating have been reported with dopamine agonists and/or other dopaminergic treatments, and rarely in patients treated with levodopa, including SINEMET[®] (see WARNINGS AND PRECAUTIONS).

Respiratory:

Dyspnea, upper respiratory infection.

Skin:

Alopecia, rash, increased sweating, dark sweat, malignant melanoma (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Skin).

Urogenital:

Dark urine, urinary frequency, urinary tract infection.

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

Body as a whole:

Fatigue.

Cardiovascular:

Myocardial infarction.

Gastrointestinal:

Sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, flatulence, burning sensation of tongue, gastrointestinal pain, heart burn.

Metabolic:

Weight gain or loss, edema.

Musculoskeletal:

Leg pain.

Nervous System/Psychiatric:

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

Respiratory:

Pharyngeal pain, cough.

Skin:

Flushing.

Special Senses:

Diplopia, blurred vision, dilated pupils, and oculogyric crises.

Urogenital:

Urinary retention, urinary incontinence, priapism.

Miscellaneous:

Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, creatinine, uric acid, and positive Coomb's test.

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

Decreased white blood cell count and serum potassium; protein and glucose in urine have been reported with levodopa alone and with various levodopa-carbidopa formulations, and may occur with SINEMET[®].

DRUG INTERACTIONS

Drug-Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with SINEMET[®]:

Antihypertensive Drugs: Symptomatic postural hypotension can occur 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.

Psychoactive Drugs: Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones, and risperidone) 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 carefully observed for loss of antiparkinsonian effect.

Concomitant therapy with selegiline and levodopa-carbidopa preparations may be associated with severe orthostatic hypotension not attributable to levodopa-carbidopa 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[®]. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

Dopamine Depleting Agents: Use of SINEMET[®] with dopamine-depleting agents (e.g., reserpine¹ and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended as reduction in patient response to levodopa may occur.

Isoniazid: Isoniazid may reduce the therapeutic effects of levodopa.

Anesthetics: When general anesthesia is required, SINEMET[®] should be discontinued the night before. Therapy with SINEMET[®] may be continued as soon as the patient is able to take medication by mouth.

Iron: Studies have demonstrated that ferrous sulphate decreases the bioavailability of carbidopa and/or levodopa. Because this interaction may be due to the formation of drug-iron complexes, other iron supplement formulations and iron-containing multivitamins may have similar effects.

Metoclopramide: 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.

Drug-Food Interactions

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

¹Not marketed in Canada

Drug-Laboratory Interactions

SINEMET[®] may cause a false-positive reaction for urinary ketone bodies when a tape test 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 with levodopa-carbidopa 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 levodopa-carbidopa therapy.

DOSAGE AND ADMINISTRATION

Dosing Considerations

In order to reduce the incidence of adverse reactions and achieve maximal benefit, therapy with SINEMET[®] (levodopa and carbidopa) must be individualized and drug administration must be continuously matched to the needs and tolerance of the patient. It should be borne in mind that the therapeutic range of SINEMET[®] is narrower than that of levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and the dosage ranges recommended should usually not be exceeded. The appearance of involuntary movements should be regarded as a sign of levodopa toxicity and as an indication of overdose, requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesias.

If a patient being treated with levodopa is switched to therapy with SINEMET[®], levodopa must be discontinued at least twelve hours or more before therapy with SINEMET[®] is initiated.

SINEMET[®] tablets are available in a 4:1 ratio (SINEMET[®] 100/25) and in a 10:1 ratio of levodopa to carbidopa (SINEMET[®] 250/25). Tablets of the two ratios may be given separately or combined as needed to provide the optimal dosage.

Studies have shown that peripheral dopa decarboxylase is saturated by carbidopa at doses between 70 to 150 mg per day. Patients receiving less than 70 mg per day of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

For patients who require only low doses of levodopa, e.g., less than 700 mg, SINEMET[®] 100/25 may be helpful.

Recommended Dose and Dosage Adjustment

Induction of Therapy in Patients Not Receiving Levodopa

Dosage is best initiated with one tablet of SINEMET[®] 100/25 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be carefully increased by one tablet every three days until the optimal dosage has been reached which does not produce dyskinesias.

While increasing the dosage during the induction period, the doses should be divided, aiming at a frequency of dosing of at least four times a day. If further titration is necessary after a daily dosage level of six tablets of SINEMET[®] 100/25 has been reached, tablets of SINEMET[®] 250/25 may be used as needed to provide the optimal dosage.

Usually no patient should receive more than 1500 mg of levodopa a day. Some patients, including those with postencephalitic parkinsonism, are more sensitive to levodopa and require specially careful dosage adjustment.

Induction of Therapy in Patient Receiving Levodopa

Levodopa must be discontinued at least twelve hours or more before SINEMET[®] is started.

A dosage of SINEMET[®] should be used that will provide approximately 20% of the previous levodopa daily dosage; this can be started in the morning after the day in which the treatment with levodopa has been stopped. For example, if a patient is receiving 4,000 mg of levodopa per day, the dosage of SINEMET[®] should not provide more than 750 mg of levodopa per day divided into four to six doses.

Tablets of SINEMET[®] 100/25 should be used to start medication for patients requiring lower dosages of levodopa.

Adjustment and Maintenance of Therapy

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 more levodopa is required, SINEMET[®] 250/25 should be substituted for SINEMET[®] 100/25. If necessary, the dosage of SINEMET[®] 250/25 may be increased by 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.

Current evidence indicates that other standard antiparkinsonian drugs may be continued while SINEMET[®] is being administered although their dosage may have to be adjusted.

If general anesthesia is required, therapy with 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.

Missed Dose

If a tablet is missed, it should be taken as soon as possible. If it is almost time to take the next tablet, the missed tablet should not be taken, and the normal schedule should be resumed.

OVERDOSAGE

Management of acute overdosage with SINEMET[®] (levodopa and carbidopa) is basically the same as management of acute overdosage with levodopa alone. However, 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 possible development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET[®] should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

For up-to-date information on the management of a suspected drug overdose, the physician should consider contacting a regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The 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 because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and is converted to dopamine in the basal ganglia. This is thought to be the mechanism whereby levodopa relieves the symptoms of Parkinson's disease.

Pharmacodynamics

When levodopa is administered orally it is rapidly converted to dopamine by decarboxylation in peripheral 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 attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in peripheral tissues.

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. Since its decarboxylase inhibiting activity is limited to peripheral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain. Combined therapy with levodopa and carbidopa reduces the amount of levodopa required for optimum therapeutic benefit by about 75–80%, permits an earlier response to therapy, and also reduces the incidence of nausea, vomiting and cardiac arrhythmias. Combined therapy, however, does not decrease adverse reactions due to central effects of levodopa.

Pharmacokinetics

At steady state, the bioavailability of carbidopa from SINEMET[®] tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa. Since levodopa competes with certain aminoacids, the absorption of levodopa may be impaired in some patients on a high protein diet.

Following simultaneous administration of carbidopa and levodopa in man, both plasma levels and plasma half-life of levodopa are markedly increased over those found when the same dosage of levodopa is given alone, while plasma levels of dopamine and homovanillic acid are reduced or do not change. Nevertheless, the plasma levels vary greatly between patients.

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.

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 B₆), 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.

STORAGE AND STABILITY

Tablets should be stored at room temperature (15 °C–30 °C). Store in tightly closed container, protected from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SINEMET[®] tablets contain levodopa and carbidopa in ratios of 4:1 and 10:1.

SINEMET[®], 100/25, contains 100 mg of levodopa and 25 mg anhydrous equivalent of carbidopa. They are yellow, round, uncoated tablets, plain on one side and “650” on the other. They are supplied in bottles of 100 tablets.

SINEMET[®], 250/25, contains 250 mg of levodopa and 25 mg anhydrous equivalent of carbidopa. They are light dapple-blue, round, uncoated tablets, plain on one side and “654” on the other. They are supplied in bottles of 100 tablets.

Non-medicinal ingredients

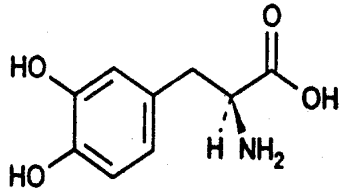
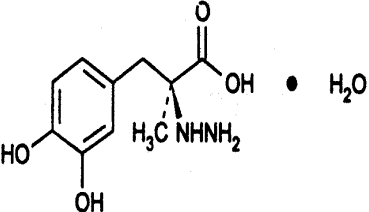
crospovidone, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

SINEMET[®] 250/25 tablets also contain FD&C Blue No. 2 Aluminum Lake. SINEMET[®] 100/25 tablets also contain D & C yellow No. 10 Lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | | |
|-----------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Proper name: | levodopa and | carbidopa |
| Chemical name: | (-)-3-(3,4-Dihydroxyphenyl)-L-alanine | (-)-L- α -Hydrazino-3,4-dihydroxy- α -methylhydrocinnamic acid mono-hydrate. |
| Molecular formula: | C ₉ H ₁₁ NO ₄ | C ₁₀ H ₁₄ N ₂ O ₄ • H ₂ O |
| Molecular mass: | 197.2 | 244.3 |
| | Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3. | |
| Structural formula: |  |  |
| Physicochemical properties: | Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water. | Carbidopa, an inhibitor of aromatic amino acid decarboxylase, is a white, crystalline compound, slightly soluble in water. |

DETAILED PHARMACOLOGY

Levodopa: Pharmacological experiments in various species of animals have shown that levodopa produced increased motor activity, aggressive behaviour and electroencephalographic alerting behaviour. However, occasional sedation and ataxia have also been reported in some animal species. Levodopa also reverses the reserpine induced Parkinson-like effects in animals. Cardiovascular studies in dogs and cats have shown that levodopa increases the catecholamine levels in the brain which has been evident in an initial increase in blood pressure followed by a secondary decrease in blood pressure. The changes in blood pressure appear to correlate with the changes in renal function. Biochemical studies *in vivo* as well as *in vitro* have demonstrated that levodopa is decarboxylated to dopamine in many tissues. Levodopa crosses the blood-brain barrier and elevates the dopamine concentration in the brain. The dopamine formed can be degraded to dihydroxyphenylacetic and homovanillic acids which are the two major metabolites in the urine. Dopamine may also be converted to noradrenaline, in which case the major metabolites are vanillylmandelic acid and dihydroxymandelic acid.

Carbidopa: In the absence of biogenic amine precursors, carbidopa is singularly inert pharmacologically. Carbidopa lacks effects upon blood pressure in normal, neurogenic

hypertensive, or renal hypertensive dogs. It also does not affect heart rate, exhibit ganglionic, adrenergic, or peripheral anticholinergic properties, or influence renal electrolyte excretion in this species. In mice or rats, carbidopa does not appreciably affect gastric secretion, nor gastric or colonic motility. The compound does not antagonize electroshock or pentylenetetrazol-induced convulsions in mice; neither does it exhibit analgesic activity or affect fixed interval-fixed ratio reinforcement behaviour in rats. Overt behavioural effects have not been observed with carbidopa in the rhesus monkey, dog, rat, mouse or pigeon. The dose levels of carbidopa used in the latter investigations were in excess of those necessary to inhibit aromatic amino acid decarboxylase or to alter the actions of levodopa. The studies suggest that carbidopa, when administered alone at dose levels effective in inhibiting aromatic amino acid decarboxylases, lacks appreciable effects upon the cardiovascular, gastrointestinal, renal, or central nervous systems.

Levodopa and Carbidopa Combination: Decarboxylation within peripheral organs and the walls of the brain capillaries limits the portion of an administered dose of levodopa accessible to most central nervous structures. Inhibition of peripheral aromatic amino acid decarboxylase enhances the accumulation of levodopa in the blood and increases the amount of this amino acid available to the brain. If brain decarboxylase is not also inhibited, the result is a marked accumulation of dopamine in the brain. Such a mechanism explains the marked enhancement of brain Dopa and dopamine levels which results when levodopa is administered in combination with carbidopa which does not penetrate central nervous system structures even when administered in high doses. Levodopa increases motor activity and irritability, and antagonizes reserpine-induced hypothermia, suppressed locomotion, and ptosis in mice. All these effects are enhanced two-to-six fold by pre-treatment with carbidopa. Increased motor activity induced by levodopa in rats also is enhanced by pre-treatment with carbidopa. In contrast, levodopa-induced vomiting is decreased significantly in dogs and pigeons by pre-treatment with carbidopa.

Metabolism: Carbidopa is incompletely absorbed in the rat, dog and rhesus monkey. Following oral administration of a dose of ¹⁴C labelled drug, the percentages of radioactive carbon excreted in urine and feces were:

| | URINE | FECES |
|---------------|--------------|--------------|
| RAT | 16 | 52 |
| DOG | 66 | 11 |
| MONKEY | 40 | 32 |

Urines contained both unchanged drug and metabolites.

Tissue distribution of radioactivity in rats, sacrificed one hour after an intravenous dose of 20 mg/kg of ¹⁴C-carbidopa, showed the major portion of radioactivity to be concentrated in the kidneys, lungs, small intestine, and liver; in descending order. None was detected in the brain. Following an oral dose of radioactive labelled carbidopa to healthy subjects and to patients with Parkinson's disease, maximal plasma levels of radioactivity were reached in two to four hours in the healthy 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% of the total urinary radioactivity. Only metabolites were present thereafter. In monkeys, an oral dose of levodopa given one hour after a dose of radioactive labelled carbidopa had no significant effect on the absorption or excretion of carbidopa. Peak plasma levels of radioactivity were achieved in the same period of time and disappeared at the same rate as with carbidopa alone.

TOXICOLOGY

Summary of Acute Oral Toxicity Data

A. Carbidopa

| Species | Sex | LD ₅₀ mg/kg | Signs of Toxicity |
|-----------|-----|------------------------|---------------------------------------|
| Rat (A&W) | F | 4810 | Ptosis, ataxia, decreased activity |
| Rat (A&W) | M | 5610 | |
| Rat (I) | M&F | 2251 | |
| Mouse (A) | F | 1750 | As above plus bradypnea |

B. Levodopa

| Species | Sex | LD ₅₀ mg/kg | Signs of Toxicity |
|---------|-----|------------------------|-------------------------------------------------------------------------------------------------------------|
| Rat (A) | F | 2260 | Vocalization, irritability, excitability, increased activity followed by decreased activity. |
| Rat (A) | M | 1780 | |
| Mouse | F | 1460 | |

C. Carbidopa/Levodopa (1:1)

| Species | Sex | LD ₅₀ mg/kg | Signs of Toxicity |
|---------|-----|------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Mouse | M&F | 1930 ^{xx} | Erect tail, piloerection, ataxia, lacrimation, increased activity and irritability, clonic convulsion. |

D. Carbidopa/Levodopa (1:3)

| Species | Sex | LD ₅₀ mg/kg | Signs of Toxicity |
|---------|-----|------------------------|-------------------|
| Mouse | M&F | 3270 ^{xx} | As above |

^{xx} Sum of individual doses of carbidopa/levodopa

A – Adult

W – Weanling

I – Infant

The preceding table summarizes the acute toxicity data for carbidopa and levodopa alone and in combination. Mortality usually occurred in 12 hours with carbidopa and 30 minutes with levodopa. With the combination of carbidopa and levodopa, deaths occurred between 30 minutes and 24 hours at high doses and up to 12 days with lower doses. The toxicity did not continue to decrease with drug ratios above 1:3.

In oral subacute toxicity studies, carbidopa is more toxic for dogs than for monkeys or rats. Following doses of 45 mg/kg/day for six weeks, dogs exhibited anorexia, emesis, tarry stools, diarrhea, dry nose and/or gums, fine muscular tremors, weight loss, prolonged clotting and prothrombin times, bilirubinuria and decreases in total leukocytes, total protein and albumin, and SGOT activity. The increased toxicity in dogs appeared to be due to pyridoxine-deficiency, since concurrent administration of pyridoxine decreased the toxicity of carbidopa. Doses up to 135 mg/kg/day produced no drug-related effects in the monkey and only flaccidity in some rats. Slight centrilobular vacuolization of hepatocytes in two rats and significantly higher mean kidney weights were observed in the highest dosage group.

Oral toxicity studies with doses of levodopa up to 1000 mg/kg/day for 13 weeks indicated no treatment-related effects in monkeys. In rats, treatment-related morphologic changes occurred in salivary glands (hypertrophy of acinar cells) and adrenals (cytoplasmic rarefaction of the zona glomerulosa) at all dosage levels, in kidneys of rats receiving 500 and 1000 mg/kg/day (tubular necrosis with regeneration and necrosis respectively) and in the stomach (focal necrosis of the superficial epithelium) of some rats in the high dosage group. A statistically significant leucocytosis and increase in heart and kidney weights occurred in females of this latter group; males had a significant increase in heart and liver weights and a decrease in growth rate. Clinical signs of toxicity included ptialism, piloerection, hyperventilation with intermittent dyspnea and decreased activity.

Combinations of carbidopa and levodopa in respective doses of 30/30, 30/60, and 30/120 mg/kg/day were given orally for 14 weeks to monkeys and for 13 weeks to rats. Signs of toxicity in monkeys were related to dosage and indicated that coadministration enhanced the pharmacologic activity of levodopa. In the rat, the apparent degree of potentiation of levodopa by carbidopa appeared to be less.

Three dosage ratios of carbidopa and levodopa were given orally to monkeys and rats for 54 weeks. Dosages of 10/20 mg/kg/day had no apparent physical effects while hyperactivity occurred in monkeys at dosages of 10/50 and 10/100 mg/kg/day, and continued for 32 weeks with the higher dose. 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. Morphological changes, where present, were those noted with levodopa alone.

Acute oral interaction studies in mice demonstrated that pre-treatment with pharmacological doses (1 mg/kg) of benztrapine mesylate or trihexyphenidyl hydrochloride did not affect the acute toxicity of carbidopa, levodopa or a 1:3 mixture of carbidopa:levodopa.

Higher doses (24–184 mg/kg) increased the acute toxicity of carbidopa and the combination but not of levodopa. Pre-treatment with an MAO inhibitor (phenelzine) resulted in a five-fold increase in acute toxicity of the mixture and a four-fold increase in toxicity of levodopa with no change in toxicity of carbidopa. Synergism between a 1:10 mixture of carbidopa:levodopa and amantadine was indicated by increased toxicity in the female mouse. However, no synergism was demonstrated between therapeutic doses of amantadine and carbidopa, levodopa or a 1:10 mixture.

Teratologic and Reproductive Studies

The incidences of malformations of the heart and great vessels were 0 of 105, 1 of 94, and 6 of 81 fetuses from rabbits given 75, 125 or 250 mg of levodopa/kg/day respectively by the oral route, indicating a dose-dependent teratogenic effect. Anomalies included septal defects, constricted or missing ductus arteriosus, enlarged aortic arches, fused aortas and pulmonary arches, and transpositions.

The same types of malformations were also induced in fetuses from rabbits given doses of various combinations of levodopa and carbidopa, but they were not observed when carbidopa was given alone. The malformations, possibly drug-related, were also seen in one mouse fetus from a dam which had received 500 mg of levodopa/kg/day. No drug-induced malformations were observed in fetuses of mice given various combinations of the two drugs or in the offspring of rats given carbidopa. The significance of heart and great vessel malformations in one stunted fetus from a female mouse given the lowest dose of carbidopa (30 mg/kg/day) and in one stillborn pup from a female rat given the mid-dose of the drug combination (10 mg of carbidopa/kg plus 50 mg of levodopa/kg/day) is questionable; both offspring also had other external, cranial and skeletal malformations.

Other effects on reproduction associated with combination treatments in the rabbit included decreased maternal weight gains and fetal weights, and increased resorptions, and incidences of various skeletal anomalies, especially of vertebral centra and skull bones. In mice given the combination product, only a decrease in fetal weight occurred. In rats, none of these effects were observed; the maximal dose administered was 10 mg of carbidopa/kg plus 100 mg of levodopa/kg/day.

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PART III: CONSUMER INFORMATION**levodopa and carbidopa tablets, USP**

This leaflet is part III of a three-part "Product Monograph" published when SINEMET[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SINEMET[®]. Contact your physician or pharmacist if you have any questions about the drug.

Remember – This medicine is prescribed for the particular condition that you have. **Do not give this medicine to other people, nor use it for any other condition.**

ABOUT THIS MEDICATION

SINEMET[®] is the brand name for the substance – levodopa and carbidopa, available **only on prescription** from your physician.

What the medication is used for:

Your physician has prescribed SINEMET[®] to treat the symptoms of Parkinson's disease.

Parkinson's disease is a chronic disorder characterized by slow and unsteady movement, muscular stiffness, and tremor. If untreated, Parkinson's disease can cause difficulty in performing normal daily activities.

What it does:

SINEMET[®] is a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor. It treats the symptoms of Parkinson's disease.

It is believed that the symptoms of Parkinson's disease are caused by a lack of dopamine, a naturally occurring chemical produced by certain brain cells. Dopamine has the role of relaying messages in certain regions of the brain that control muscle movement. Difficulty in movement results when too little dopamine is produced.

Levodopa acts to replenish dopamine in the brain, while carbidopa ensures that enough levodopa gets to the brain where it is needed. In many patients, this reduces the symptoms of Parkinson's disease.

When it should not be used:

Do not take SINEMET[®], if you:

- are allergic to any of its ingredients
- have any suspicious skin lesions (moles) which have not been examined by your physician or if you have ever had skin cancer
- are being treated with certain MAO inhibitor drugs, such as for depression, within the last 2 weeks
- have narrow-angle glaucoma
- have untreated heart, liver, kidney, lung, blood or hormonal disease
- have been told that you should not take sympathomimetic drugs such as isoproterenol, amphetamines, epinephrine or cough and cold medications containing drugs related to epinephrine

What the medicinal ingredients are:

Levodopa and carbidopa

What the non-medicinal ingredients are:

Croscopovidone, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch.

SINEMET[®] 250/25 tablets also contain FD&C Blue No. 2 Aluminum Lake. SINEMET[®] 100/25 tablets also contain D & C yellow No. 10 Lake.

What dosage forms it comes in:

Tablets (levodopa/carbidopa): 100 mg/25 mg (yellow), and 250/25 (light dapple-blue).

WARNINGS AND PRECAUTIONS

Some people feel sleepy, drowsy, or, rarely, may suddenly fall asleep without warning (i.e. without feeling sleepy or drowsy) when taking SINEMET[®]. During treatment with SINEMET[®] take special care when you drive or operate a machine. If you experience excessive drowsiness or a sudden sleep onset episode, refrain from driving and operating machines, and contact your physician.

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. Therefore, patients treated with SINEMET[®] should have periodic skin examinations.

BEFORE taking SINEMET[®], tell your physician or pharmacist if you:

- have or have had any medical conditions including: allergies; depression or mental disturbances; lung, kidney, liver, heart or hormonal problems; skin cancer or suspicious skin lesions; ulcer in your gut (called "duodenal" or "peptic ulcer"); convulsions/seizures; or glaucoma
- have previously been treated with levodopa
- are pregnant or plan to become pregnant
- are breastfeeding or wish to breastfeed
- are going to have an operation that requires general anesthesia
- drive or operate machinery

Tell your doctor if you or your family member/caregiver notices you are developing urges to gamble, increased sexual urges, excessive eating or spending, and/or other intense urges that could harm yourself or others. These behaviors are called impulse control disorders. Your doctor may need to review your treatments.

It is not recommended to use SINEMET[®] while you are pregnant or breast-feeding.

It is not known what effect SINEMET[®] may have on human pregnancy. Levodopa, one of the components of SINEMET[®], is passed into human milk. If you are pregnant, may become pregnant or intend to breast-feed, tell your physician, who will help you weigh the benefits of the drug for you against possible risks to your baby. As you improve on SINEMET[®], you may increase your physical activity gradually and with caution related to any other medical conditions you may have.

SINEMET[®] should not be given to children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Although SINEMET[®] can generally be given with other medicines, there are exceptions. Tell your physician about all medicines you are taking or plan to take, including those obtained without a prescription.

It is particularly important to tell your physician if you are taking:

- antihypertensive drugs (used to treat elevated blood pressure)
- some medications used to treat psychiatric conditions or mental depression (including phenothiazines, butyrophenones, risperidone, selegiline, tricyclic antidepressants and monoamine oxidase inhibitors)
- tetraabenazine (medication used to treat conditions related to involuntary movements such as Huntingtons Disease)
- phenytoin (anti-epileptic medication)
- papaverine (medication for intestinal spasms)
- isoniazid (medication to treat tuberculosis)
- metoclopramide (for nausea and vomiting)
- iron salts (such as multivitamins tablets) which may reduce the amount of carbidopa and/or levodopa available to the body

A change in diet to foods that are high in protein (such as meat, fish, dairy products, seeds and nuts) may delay the absorption of levodopa and SINEMET[®] may not work as well as it should.

PROPER USE OF THIS MEDICATION

Usual dose:

The dosage of SINEMET[®] is variable and your physician will adjust it according to the severity of your disease and your response to treatment.

SINEMET[®] is an immediate-release formulation of levodopa-carbidopa that is designed to begin release of ingredients within 30 minutes. For best results take SINEMET[®] every day. It is important to carefully follow your physician's advice on how much SINEMET[®] to take and how often to take it. Promptly inform your physician of any change in your condition such as nausea or abnormal movements, as this may require an adjustment in your prescription.

Do not change the dose regimen prescribed by your physician and do not add any additional antiparkinson medications, including other levodopa-carbidopa preparations, without first consulting your physician.

Do not stop taking this medicine abruptly or lower the dosage without checking with your physician. If you suddenly stop or reduce your dosage you may experience the following symptoms: stiff muscles, high temperature (fever) and mental changes.

Overdose:

In case of an overdose, contact your physician immediately so that medical attention may be given promptly.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Missed Dose:

Try to take SINEMET[®] as prescribed. However, if you have missed a dose, take it as soon as you remember. If it is almost time to take your next tablet, do not take the missed tablet, but resume your normal schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

SINEMET[®] is generally well tolerated. Like any other medicine, however, SINEMET[®] may have unintended or undesirable effects, so called side-effects.

Very rare but serious side effects that have been reported include sudden sleep onset episodes (see WARNINGS AND PRECAUTIONS).

Certain side effects that have been reported with SINEMET[®] may affect some patients' ability to drive or operate machinery.

SINEMET[®] can cause somnolence (excessive drowsiness) and sudden sleep onset episodes. Therefore you must refrain from driving or engaging in activities where impaired alertness may put yourself or others at risk of injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see WARNINGS AND PRECAUTIONS).

The most frequent side effects are: abnormal movements including twitching or spasms (which may or may not resemble your Parkinson's symptoms), and nausea.

Other possible side effects include: mental changes, dream abnormalities, hair loss, diarrhea, dizziness, vomiting, loss of appetite, and slow movement (see WARNINGS AND PRECAUTIONS). Occasionally, dark colour (red, brown or black) may appear in your saliva, urine or sweat after you take SINEMET[®].

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptoms / Effects | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------|-----------------------------------------------------|
| | | Only if severe | In all cases | |
| Most Common | Abnormal involuntary movements, such as spasms or twitching | | ✓ | |
| Common | Hallucinations (seeing or hearing things that are not there) | | ✓ | |
| Rare | Allergic reactions [red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing or swallowing] | | | ✓ |
| | Excessive sleepiness; Falling asleep without warning | | ✓ | |
| | Impulse control symptoms (inability to resist the impulse to perform an action that could be harmful) such as compulsive gambling, increased sexual urges, and/or behaviours, uncontrollable excessive shopping or spending, binge/ compulsive eating, and/or other urges | | ✓ | |
| | Changed patches of pigmented skin, including irritated or irregular moles, or moles in which you have noticed changes (melanoma) | | ✓ | |
| | Uneven (irregular) heart beat or palpitations | | ✓ | |
| | Feeling of lightheaded-ness as when standing quickly | | ✓ | |

This is not a complete list of side effects. For any unexpected effects while taking SINEMET[®], contact your doctor or pharmacist.

HOW TO STORE IT

Store your tablets at room temperature (15 °C–30 °C). Store in tightly closed container, protected from light and moisture.

Keep all medicines out of the reach of children.

Do not use outdated medicine.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or

Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about SINEMET[®]:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the [Health Canada website](http://www.healthcanada.gc.ca) or Merck Canada web site www.merck.ca or by calling Merck Canada at 1-800-567-2594

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