

PRODUCT MONOGRAPH

SINEMET[®] CR

levodopa and carbidopa controlled release tablets

100 mg/25 mg

100 mg levodopa and 25 mg carbidopa

200 mg/50 mg

200 mg levodopa and 50 mg carbidopa

Antiparkinson Agent

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▣ SINEMET® CR

levodopa and carbidopa controlled release tablets

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, 200 mg/50 mg	For a complete listing, see <i>DOSAGE FORMS, COMPOSITION AND PACKAGING</i> section.

INDICATIONS AND CLINICAL USE

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

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

Pediatrics (< 18 years of age):

The safety and effectiveness of SINEMET® CR 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® CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET® CR. SINEMET® CR 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[®] CR 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[®] CR 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[®] CR 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[®] CR (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[®] CR, 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[®] CR 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[®] CR. 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.

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.

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.

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 are receiving levodopa monotherapy or SINEMET[®] (levodopa and carbidopa), this medication must be discontinued at least 8 hours before therapy with SINEMET[®] CR is started. (For appropriate dosage substitutions, see DOSAGE AND ADMINISTRATION.)

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy (see ADVERSE REACTIONS).

Physical Activity

Patients who improve while on therapy with SINEMET[®] CR 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[®] CR to patients with a history of recent 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 administration and titration, in a facility with provisions for intensive cardiac care.

Gastrointestinal

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

Neurologic

As with levodopa or SINEMET[®], SINEMET[®] CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. These adverse reactions may be more prolonged with SINEMET[®] CR than with SINEMET[®].

SINEMET[®] CR 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[®] CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Psychomotor Performance

Certain side effects that have been reported with SINEMET[®] CR 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[®] CR. 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

Patients with chronic wide angle glaucoma may be treated cautiously with SINEMET[®] CR (levodopa and carbidopa), provided the intraocular pressure is well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Peri-Operative Considerations

If general anesthesia is required, SINEMET[®] CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Interruption of Therapy).

Psychiatric

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.

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[®] CR (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[®] CR 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[®] CR 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[®] CR 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[®] CR 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): Safety of SINEMET[®] CR 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 (see ADVERSE REACTIONS).

SINEMET[®] CR 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 Adverse Drug Reactions

In controlled clinical trials involving 748 patients with moderate to severe motor fluctuations, SINEMET[®] CR (levodopa and carbidopa) did not produce side effects which were unique to the controlled release formulation.

The adverse reaction reported most frequently was dyskinesia (12.8%). Occasionally, prolonged, and at times, severe afternoon dyskinesias have occurred in some patients.

Other adverse reactions that were reported frequently were: nausea (5.5%), hallucinations (5.3%), confusion (4.9%), dizziness (3.5%), headache (2.5%), depression (2.5%), chorea (2.5%), dry mouth (2.3%), somnolence (2.1%), including very rarely excessive daytime somnolence and sudden sleep onset episodes, dream abnormalities (2.1%), dystonia (2.0%) and asthenia (2.0%).

Adverse reactions occurring less frequently (less than 2%) were:

System	%
Body as a whole	
Chest pain	1.7
Fatigue	0.9
Weight loss	0.8
Cardiovascular	
Orthostatic hypotension	0.8
Palpitation	0.8
Hypotension	0.5
Nervous System / Psychiatric	
Insomnia	1.7
Falling	1.6
On-off phenomenon	1.2
Paresthesia	0.9
Disorientation	0.8
Anxiety disorders	0.8
Decreased mental acuity	0.7
Extrapyramidal disorder	0.7
Gait abnormalities	0.7
Agitation	0.5
Memory impairment	0.5
Gastrointestinal	
Anorexia	1.9
Constipation	1.5
Vomiting	1.3
Diarrhea	1.2
Gastrointestinal pain	0.9
Dyspepsia	0.8
Musculoskeletal	
Muscle cramps	0.9
Respiratory	
Dyspnea	1.6
Special Senses	
Blurred vision	1.1

Other adverse reactions reported in clinical trials or in post-marketing experience include: orthostatic effects, hypertension, myocardial infarction, cardiac irregularities, syncope, hypotensive episodes, dysphagia, heartburn, taste alterations, dark saliva, leg pain, shoulder pain, back pain, angioedema, urticaria, pruritus, bullous lesions (including pemphigus-like reactions), nervousness, sleep disorders, neuroleptic malignant syndrome (see WARNINGS AND PRECAUTIONS), increased tremor, peripheral neuropathy, psychotic episodes including delusions and paranoid ideation, cough, pharyngeal pain, common cold, upper respiratory

infection, blurred vision, flushing, alopecia, rash, dark sweat, dark urine, urinary incontinence, urinary frequency, urinary tract infection, malignant melanoma (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Skin).

Behavioural Changes:

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[®] CR (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

Other adverse reactions that have been reported with levodopa or SINEMET[®] and may be potential side effects with SINEMET[®] CR are listed below.

Cardiovascular:

Arrhythmias, non-specific ECG changes, phlebitis.

Gastrointestinal:

Sialorrhea, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

Genitourinary:

Urinary retention, hematuria, and priapism.

Hematologic:

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

Hypersensitivity:

Henoch-Schoenlein purpura.

Nervous System/Psychiatric:

Ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as a early sign of excess dosage, consideration of dosage reduction may be needed at this time), trismus, activation of latent Horner's syndrome, euphoria and dementia, depression with suicidal tendencies, bradykinetic episodes.

Skin:

Increased sweating, pruritus.

Special Senses:

Diplopia, dilated pupils, oculozyric crises.

Miscellaneous:

Weight gain, edema, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns.

Convulsions have occurred; however, a causal relationship with levodopa or levodopa/carbidopa combinations has not been established.

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[®] CR.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Antihypertensive Drugs: Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment of patients receiving antihypertensive drugs. Therefore, when therapy with SINEMET[®] CR 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[®] CR should be observed carefully for loss of therapeutic response.

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 carbidopa-levodopa preparations. (For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.)

Dopamine Depleting Agents: Use of SINEMET[®] CR 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[®] CR should be discontinued the night before. Therapy with SINEMET[®] CR 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.

Other Drugs: Although specific interaction studies were not performed with other concomitant drugs, in clinical trials of SINEMET[®] CR patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, thiazides, angiotensin converting enzyme inhibitors, calcium channel blockers, digoxin, H₂ antagonists, salicylates and other nonsteroidal anti-inflammatory drugs. SINEMET[®] CR was also used with other antiparkinson agents (see DOSAGE AND ADMINISTRATION).

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.

Drug-Laboratory Interactions

SINEMET[®] CR 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.

¹Not marketed in Canada

DOSAGE AND ADMINISTRATION

Dosing Considerations

SINEMET[®] CR (levodopa and carbidopa) tablets contain a 4:1 ratio of levodopa to carbidopa. SINEMET[®] CR 200/50 contains levodopa 200 mg/carbidopa 50 mg (anhydrous equivalent) per tablet. SINEMET[®] CR 100/25 contains levodopa 100 mg/carbidopa 25 mg (anhydrous equivalent) per tablet. The daily dosage of SINEMET[®] CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

SINEMET[®] CR should only be administered as whole tablets. To maintain the controlled release properties of the product, tablets should not be chewed or crushed.

Standard antiparkinson drugs, other than levodopa alone, may be continued while SINEMET[®] CR is being administered, although their dosage may have to be adjusted. The delayed onset of action with SINEMET[®] CR may require the supplemental use of conventional SINEMET[®] tablets for optimal control in the mornings.

Recommended Dose and Dosage Adjustment

Initial Dosage and Titration for Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations

Dosage with SINEMET[®] CR 200/50 should be substituted at an amount that eventually provides approximately 10 to 30 percent more levodopa per day. The interval between doses should be prolonged by 30 to 50 percent. Initially, patients should receive SINEMET[®] CR 200/50 at a dosage that provides the same amount of levodopa, but with a longer dosing interval. Depending on clinical response, the dosage may be increased.

A guide for the initiation of treatment with SINEMET[®] CR is shown in the following table:

Guideline for Initial Conversion from SINEMET[®] to SINEMET[®] CR

SINEMET[®] Total Daily Dose* Levodopa (mg)	SINEMET[®] CR Suggested Dosage Regimen
300–400	1 tablet 200/50 b.i.d.
500–600	1 tablet 200/50 plus 1 tablet 100/25 b.i.d. or 1 tablet 200/50 t.i.d.
700–800	1 tablet 200/50 plus 1 tablet 100/25, in the a.m., 1 tablet 200/50 plus 1 tablet 100/25, in the early p.m., 1 tablet 200/50, in the later p.m.
900–1000	2 tablets 200/50, in the a.m. 2 tablets 200/50, in the early p.m. 1 tablet 200/50 in the later p.m.

*For dosing ranges not shown in the table, see DOSAGE AND ADMINISTRATION.

SINEMET[®] CR 100/25 is available to facilitate titration when 100 mg steps are required.

Initial Dosage for Patients Currently Treated with Levodopa Alone

Levodopa must be discontinued at least eight hours before therapy with SINEMET[®] CR 200/50 is started. SINEMET[®] CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET[®] CR 200/50 two times daily.

Patients Without Prior Levodopa Therapy

SINEMET[®] CR 100/25 may be used in early stage patients who have not had prior levodopa therapy or to facilitate titration when necessary in patients receiving SINEMET[®] CR 200/50. The initial recommended dose is 1 tablet of SINEMET[®] CR 100/25 twice daily. For patients who require more levodopa, a daily dose of 1 to 4 tablets of SINEMET[®] CR 100/25 twice a day is generally well-tolerated.

When appropriate, levodopa therapy may also be initiated with SINEMET[®] CR 200/50. The initial recommended dose in patients with mild to moderate disease is 1 tablet of SINEMET[®] CR

200/50 two times daily. Initial dosages should not exceed 600 mg per day of levodopa or be given at intervals of less than 6 hours.

Titration

Doses and dosing intervals must be adjusted on an individual basis, depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended. Most patients have been adequately treated with 2 to 8 tablets of SINEMET[®] CR 200/50 per day, administered as divided doses at intervals ranging from 4 to 12 hours during the waking day.

If the divided doses of SINEMET[®] CR 200/50 are not equal, it is recommended that the smaller doses be given at the end of the day.

Maintenance

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of SINEMET[®] CR may be required.

Addition of other Antiparkinson Medications

Anticholinergic agents, dopamine agonists, amantadine and lower doses of selective MAO-B inhibitors can be given with SINEMET[®] CR. When combining therapies, dosage adjustments may be necessary.

Interruption of Therapy

Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET[®] CR is required, especially if the patient is receiving neuroleptics (see WARNINGS AND PRECAUTIONS).

If general anesthesia is required, SINEMET[®] CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

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[®] CR (levodopa and carbidopa) is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET[®] CR.

Electrocardiographic monitoring should be instituted and the patient observed carefully for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET[®] CR should be

taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

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

SINEMET[®] CR (levodopa and carbidopa), a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor, is available in a polymer-based controlled-release tablet formulation. SINEMET[®] CR can be useful in reducing "off" time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had predictable peak dose dyskinesias and unpredictable motor fluctuations.

The symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. While the administration of dopamine is ineffective in the treatment of Parkinson's disease because it does not cross the blood-brain barrier, 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

Levodopa is rapidly decarboxylated to dopamine 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, a decarboxylase inhibitor, 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.

Following years of treatment with preparations containing levodopa, an increasing number of parkinsonian patients develop fluctuations in motor performance and dyskinesias. The advanced form of motor fluctuations ('on-off' phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely

understood, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

In clinical trials, patients with motor fluctuations experienced reduced "off" time with SINEMET[®] CR when compared with SINEMET[®]. Global ratings of improvement and activities of daily living in the "on" and "off" states, as assessed by both patient and physician, were slightly better in some patients during therapy with SINEMET[®] CR than with SINEMET[®]. In patients without motor fluctuations, SINEMET[®] CR provided therapeutic benefit similar to SINEMET[®] but with less frequent dosing.

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.

Pharmacokinetics

SINEMET[®] CR 200/50 contains levodopa, 200 mg and carbidopa, 50 mg (anhydrous equivalent), per tablet, in a controlled-release formulation designed to release the active ingredients over a 4- to 6-hour period.

The absorption of levodopa following SINEMET[®] CR 200/50 is gradual and continuous for 4 to 5 hours although the majority of the dose is absorbed in 2 to 3 hours. With conventional SINEMET[®] Tablets, absorption is rapid and is virtually complete in 2 to 3 hours. The pharmacokinetic parameters of levodopa, following the administration of SINEMET[®] CR 200/50 and conventional SINEMET[®] Tablets to healthy elderly volunteers, are presented in Table 1.

Table 1 – Mean Pharmacokinetic Parameters Of Levodopa Following The Administration Of Two SINEMET® 100/25 Tablets Or One SINEMET® CR 200/50 Tablet In Healthy Elderly Volunteers

	Single Dose		Steady-State	
	SINEMET®	SINEMET® CR 200/50	SINEMET®	SINEMET® CR 200/50
Bioavailability* %	-	-	99	71
C _{max} , µg/mL	3.26	1.15	3.20	1.14
Trough Cp at 8 hr, µg/mL	0.048	0.090	0.074	0.163
Peak time, hr	0.5	2.1	0.7	2.4
AUC, µg•hr/mL	5.31	4.01	5.62	4.19

* Relative to an intravenous dose

In general, peak levodopa plasma levels are lower, bioavailability is less and time to reach peak levels is delayed when using SINEMET® CR. Levodopa plasma levels following a single dose are essentially identical to those following repeated administration. However, with SINEMET® CR, levodopa plasma concentrations fluctuate less, namely peak plasma levels are lower and end of dose levels (trough concentrations) higher than after conventional therapy.

The bioavailability of SINEMET® CR is somewhat increased in the presence of food. Dose-proportionality has been demonstrated over the dose range of one and two SINEMET® CR 200/50 Tablets.

The pharmacokinetics of levodopa following administration of SINEMET® CR 100/25 were studied in patients with Parkinson's disease. Chronic three month, open-label, twice daily dosing with SINEMET® CR 100/25 (range: 200 mg levodopa, 50 mg carbidopa up to 600 mg levodopa, 150 mg carbidopa per day) did not result in accumulation of plasma levodopa. The dose-adjusted bioavailability for one SINEMET® CR 100/25 tablet was equivalent to that for one SINEMET® CR 200/50 tablet. The mean peak concentration of levodopa following the administration of one SINEMET® CR 100/25 tablet was greater than 50% of that following one SINEMET® CR 200/50 tablet. Mean time-to-peak plasma levels may be slightly less for SINEMET® CR 100/25 than for SINEMET® CR 200/50.

Elimination half-life of levodopa in the presence of carbidopa is about 1.5 hours. Following SINEMET® CR, the apparent half-life of levodopa may be prolonged because of continuous absorption.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

SINEMET[®] CR is a controlled-release formulation of levodopa and carbidopa, in a ratio of 4:1. The tablet contains a polymer-based drug delivery system which controls the release of levodopa and carbidopa as it slowly erodes.

SINEMET[®] CR 100/25 is a dappled purple, oval-shaped, compressed tablet, engraved 601 on one side and plain on the other. Available in bottles of 100.

SINEMET[®] CR 200/50 is a dappled purple, oval-shaped, compressed tablet, engraved 521 on one side and plain on the other. Available in bottles of 100.

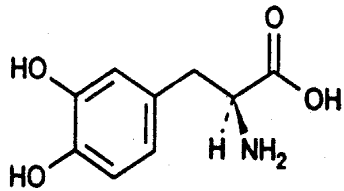
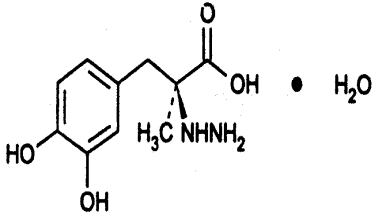
Non-medicinal ingredients: hydroxypropylcellulose, hypromellose and magnesium stearate.

SINEMET[®] CR 100/25 and SINEMET[®] CR 200/50 tablets contain FD&C Blue No.2 Aluminum Lake and FD&C Red No.40 Aluminum 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 monohydrate.
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 centrolobular 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

Pr **SINEMET® CR**
levodopa and carbidopa controlled release tablets

This leaflet is part III of a three-part “Product Monograph” published when SINEMET® CR 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® CR. 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® CR 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® CR 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® CR is a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor, in a controlled-release tablet. It treats the symptoms of Parkinson’s disease.

SINEMET® CR tablets are formulated to slowly release the two active ingredients, levodopa and carbidopa.

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. The controlled release formula keeps the amount of levodopa in your body as even as possible.

When it should not be used:

Do not take SINEMET® CR, if you:

- are allergic to any of its ingredients
- have any suspicious skin lesions (moles) which have not been examined by your doctor 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 ingredient is:

Levodopa and carbidopa

What the non-medicinal ingredients are:

Hydroxypropylcellulose, hypromellose and magnesium stearate.

SINEMET® CR 100/25 and SINEMET® CR 200/50 tablets contain FD&C Blue No.2 Aluminum Lake and FD&C Red No.40 Aluminum Lake.

What dosage forms it comes in:

Controlled release tablets (levodopa/carbidopa): 100mg/25mg (dappled purple) and 200/50 (dappled purple).

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® CR. During treatment with SINEMET® CR 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® CR should have periodic skin examinations.

Before taking SINEMET® CR, 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[®] CR while you are pregnant or breast-feeding.

It is not known what effect SINEMET[®] CR may have on human pregnancy. Levodopa, one of the components of SINEMET[®] CR, 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[®] CR, you may increase your physical activity gradually and with caution related to any other medical conditions you may have.

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

INTERACTIONS WITH THIS MEDICATION

Although SINEMET[®] CR 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)
- tetrabenazine (medications 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) 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[®] CR may not work as well as it should.

PROPER USE OF THIS MEDICATION

Usual dose:

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

SINEMET[®] CR is a sustained-release formulation of levodopa-carbidopa which releases these ingredients over a 4- to 6- hour period.

The effect of the first morning dose of SINEMET[®] CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET[®] (levodopa-

carbidopa). Consult your physician if such delayed responses pose a problem in treatment.

SINEMET[®] CR should only be administered as whole tablets. In order to maintain the slow-release properties of SINEMET[®] CR, do not chew or crush the tablets.

For best results take SINEMET[®] CR every day. It is important to carefully follow your physician's advice on how much SINEMET[®] CR 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[®] CR 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[®] CR is generally well tolerated. Like any other medicine, however, SINEMET[®] CR 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[®] CR may affect some patients' ability to drive or operate machinery.

SINEMET[®] CR 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 (which may or may not resemble your Parkinson’s symptoms), nausea, hallucinations, confusion, dizziness, and dry mouth.

Other possible side effects include: abnormal dreams or difficulty sleeping, mental changes, depression, weakness, vomiting, and loss of appetite, flushing, and hair loss (see WARNINGS AND PRECAUTIONS). Occasionally, dark color (red, brown or black) may appear in your saliva, urine, sweat after you take SINEMET® CR.

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)		✓	
	Feeling of lightheadedness when standing quickly; fainting		✓	
Rare	Allergic reactions [red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing or swallowing]			✓
	Falling asleep without warning		✓	

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	
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		✓	

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

HOW TO STORE IT

Store your tablets at room temperature (15°C and 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 SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
 - Health Canada
 - Postal Locator 0701C
 - Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-800-369-3090, or
 - Mail to: Merck Canada Inc.
 - P.O. Box 1005
 - Pointe-Claire–Dorval, QC H9R 4P8

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.

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MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.merck.ca>

or by contacting the sponsor, Merck Canada Inc., at: 1-800-567-2594

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