PRODUCT MONOGRAPH

[Pr]LEVOCARB CR

Levodopa and Carbidopa Controlled-Release Tablets

100 mg/25 mg and 200 mg/50 mg

Antiparkinson Agent

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Control No. 143936

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100 mg/25 mg and 200 mg/50 mg

PART I: HEALTH PROFFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 100 mg/25 mg, 200 mg/50 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

LEVOCARB CR is not recommended for the treatment of drug-induced extrapyramidal reactions

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with LEVOCARB CR (levodopa and carbidopa). These inhibitors must be discontinued at least two weeks prior to initiating therapy with LEVOCARB CR. LEVOCARB CR may be administered concomitantly with a MAO inhibitor with selectivity for MAO type B (e.g. selegiline HCl) (see PRECAUTIONS, Drug Interactions, Psychoactive Drugs) at the manufacturer's recommended dose which maintains selectivity for MAO type B.

LEVOCARB 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, LEVOCARB CR should not be given when administration of a sympathomimetic amine is contraindicated.

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For the complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

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

WARNINGS AND PRECAUTIONS

When patients are receiving levodopa monotherapy or levodopa/carbidopa immediate-release tablets, this medication must be discontinued at least 8 hours before therapy with LEVOCARB CR (levodopa and carbidopa) is started. (For appropriate dosage substitutions, see DOSAGE AND ADMINISTRATION).

As with levodopa or levodopa/carbidopa immediate-release tablets, levodopa/carbidopa controlled-release tablets 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 levodopa/carbidopa controlled-release tablets than with levodopa/carbidopa immediate-release tablets. 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.

Neuroleptic Malignant Syndrome

A symptom complex resembling the neuroleptic malignant syndrome, including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of levodopa/carbidopa controlled-release tablets is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Somnolence and episodes of sleep onset has been associated with levodopa. There have been very rare reports of sudden onset of sleep during daily activities, in some cases without awareness or warning signs. Patients should be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines.

Care should be exercised in administering levodopa/carbidopa controlled-release tablets to patients with a history of myocardial infarction or 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.

Levodopa/carbidopa controlled-release tablets should be administered cautiously to patients with a history of peptic ulcer disease due to the possibility of upper gastrointestinal hemorrhage

Levodopa/carbidopa controlled-release tablets should be used cautiously in patients who have a history of seizures or have conditions associated with seizure or have a lowered seizure threshold.

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

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

Use in Children
Safety of levodopa/carbidopa controlled-release tablets in patients under 18 years of age has not been established.

Use in Pregnancy and Lactation
Although the effects of levodopa/carbidopa controlled-release tablets on human pregnancy and lactation are unknown, both levodopa and combinations of levodopa and carbidopa have caused visceral and skeletal malformations in rabbits (see TOXICOLOGY, Teratologic and Reproductive Studies). Therefore, use of levodopa/carbidopa controlled-release tablets in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against the possible hazards to the mother and to the fetus.

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. Levodopa/ carbidopa controlled-release tablets should not be given to nursing mothers unless the anticipated benefits to the mother outweigh the potential hazards to the infant.

Laboratory Tests
Levodopa/carbidopa controlled-release tablets 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.

ADVERSE REACTIONS

In controlled clinical trials involving 748 patients with moderate to severe motor fluctuations, levodopa/carbidopa controlled-release tablets 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

System	%
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), increased tremor, peripheral neuropathy, increased libido, 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.

Other adverse reactions that have been reported with levodopa or levodopa/carbidopa immediate-release tablets and may be potential side effects with LEVOCARB CR are listed below:

Nervous System/Psychiatric
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 needed at this time), trismus, activation of latent Horner's syndrome, euphoria and dementia, depression with suicidal tendencies, bradykinetic episodes.

Cardiovascular
Arrhythmias, non-specific ECG changes, phlebitis.

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

Skin
Increased sweating, malignant melanoma (see CONTRAINDICATIONS).

Hypersensitivity
Henoch-Schonlein purpura.

Genitourinary
Urinary retention, hematuria and priapism.

Special Senses
Diplopia, dilated pupils, oculogyric crises.

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

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.

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

Decreased hemoglobin, hematocrit, white blood cell count and serum potassium have been reported as well as bacteria, blood, protein and glucose in the urine.

Abnormalities in various laboratory tests have occurred with levodopa/carbidopa immediate-release tablets, and may also occur with levodopa/carbidopa controlled-release tablets.

DRUG INTERACTIONS

Caution should be exercised when the following drugs are administered concomitantly with levodopa/carbidopa controlled-release tablets:

Antihypertensive Drugs: Symptomatic postural hypotension has occurred when levodopa/ decarboxylase inhibitor combinations were added to the treatment of patients receiving anti-hypertensive drugs. Therefore, when therapy with levodopa/carbidopa controlled-release tablets is started, dosage adjustment of the antihypertensive drug may be required.

Psychoactive Drugs: Dopamine D_2 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 levodopa/carbidopa controlled-release tablets 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 levodopa/carbidopa preparations. (For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS).

Isoniazid: Isoniazid may reduce the therapeutic effects of levodopa.

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

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 levodopa/carbidopa controlled-release tablets, patients were allowed to receive tricyclic antidepressants, benzodiazepines, propranolol, thiazides, angiotensin converting enzyme inhibitors, calcium channel blockers, digoxin, H_2 antagonists, salicylates and other nonsteroidal anti-inflammatory drugs. Levodopa/carbidopa controlled-release tablets were also used with other antiparkinson agents (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

LEVOCARB CR (levodopa and carbidopa) tablets contain a 4:1 ratio of levodopa to carbidopa. LEVOCARB CR 200 mg/50 mg contains levodopa 200 mg/carbidopa 50 mg per tablet. LEVOCARB CR 100 mg/25 mg contains levodopa 100 mg/carbidopa 25 mg per tablet. The daily dosage of LEVOCARB 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.

LEVOCARB CR 200 mg/50 mg may be administered as a whole or as half tablets. LEVOCARB CR 100 mg/25 mg 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 LEVOCARB CR is being administered although their dosage may have to be adjusted. The delayed onset of action with LEVOCARB CR may require the supplemental use of conventional LEVOCARB Tablets for optimal control in the mornings.

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

Dosage with LEVOCARB CR 200 mg/50 mg 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 LEVOCARB CR 200 mg/50 mg 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 LEVOCARB CR 200 mg/50 mg is shown in the following table:

Guideline for Initial Conversion from LEVOCARB to LEVOCARB CR 200 mg/50 mg	
LEVOCARB	**LEVOCARB CR 200 mg/50 mg (levodopa 200 mg/carbidopa 50 mg)**
Total Daily Dose* Levodopa (mg)	**Suggested Dosage Regimen**
300 - 400	1 tablet b.i.d.
500 - 600	1½ tablets b.i.d. or 1 tablet t.i.d.
700 - 800	A total of 4 tablets in 3 or more divided doses (e.g., 1½ tablets a.m., 1½ tablets early p.m., and 1 tablet later p.m.)
900 - 1000	A total of 5 tablets in 3 or more divided doses (e.g., 2 tablets a.m., 2 tablets early p.m., and 1 tablet later p.m.)

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

LEVOCARB CR 100 mg/25 mg is available to facilitate titration when 100 mg steps are required and as an alternative to the half tablet of LEVOCARB CR 200 mg/50 mg tablets.

Initial Dosage for Patients Currently Treated with Levodopa Alone

Levodopa must be discontinued at least eight hours before therapy with LEVOCARB CR 200 mg/50 mg is started. LEVOCARB 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 LEVOCARB CR 200 mg/50 mg two times daily.

Patients Without Prior Levodopa Therapy

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

When appropriate, levodopa therapy may also be initiated with LEVOCARB CR 200 mg/50 mg. The initial recommended dose in patients with mild to moderate disease is 1 tablet of LEVOCARB CR 200 mg/50 mg 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 levodopa/carbidopa controlled-release 200 mg/50 mg tablets per day, administered as divided doses at intervals ranging from 4 to 12 hours during the waking day.

If the divided doses of LEVOCARB CR 200 mg/50 mg 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 LEVOCARB 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 levodopa/carbidopa controlled-release tablets. When combining therapies, dosage adjustments may be necessary.

Interruption of Therapy:
Patients should be observed carefully if abrupt reduction or discontinuation of LEVOCARB CR is required, especially if the patient is receiving neuroleptics (see PRECAUTIONS).

If general anesthesia is required, LEVOCARB 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.

OVERDOSAGE

Management of acute overdosage with levodopa/carbidopa controlled-release tablets is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of levodopa/carbidopa controlled-release tablets.

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 levodopa/carbidopa controlled-release tablets should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

ACTION AND CLINICAL PHARMACOLOGY

LEVOCARB 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. Levodopa/Carbidopa controlled-release tablets 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.

Levodopa is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral 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 levodopa/carbidopa controlled-release tablets when compared with levodopa/carbidopa immediate-release tablets. 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 levodopa/carbidopa controlled-release tablets than with levodopa/carbidopa immediate-release tablets. In patients without motor fluctuations, levodopa/carbidopa controlled-release tablets provided therapeutic benefit similar to levodopa/carbidopa immediate-release tablets, but with less frequent dosing.

Pyridoxine hydrochloride (vitamin B_6), 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

Levodopa and carbidopa combination in the controlled-release formulation, 200 mg/50 mg, contains levodopa, 200 mg, and carbidopa, 50 mg, per tablet. The controlled-release formulation is designed to release the active ingredients over a 4- to 6-hour period.

The absorption of levodopa following levodopa/ carbidopa controlled-release tablets, 200 mg/50 mg, is gradual and continuous for 4 to 5 hours, although the majority of the dose is absorbed in 2 to 3 hours. With conventional levodopa/carbidopa immediate-release tablets, absorption is rapid and is virtually complete in 2 to 3 hours. The pharmacokinetic parameters of levodopa, following the administration of levodopa/carbidopa controlled-release tablets, 200 mg/50 mg, and conventional levodopa/carbidopa immediate-release tablets to healthy, elderly volunteers, are presented in the following table:

Mean pharmacokinetic parameters of levodopa following the administration of two Levodopa/Carbidopa 100/25 mg Tablets or one Levodopa/Carbidopa 200/50 mg Tablet in healthy elderly volunteers.

	Single Dose		Steady State	
	Immediate-Release 2 x 100 mg/25 mg	Controlled-Release 200 mg/50 mg	Immediate-Release 2 x 100 mg/25 mg	Controlled-Release 200 mg/50 mg
Boavailability* %	--	--	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 levodopa/carbidopa controlled-release tablets. Levodopa plasma levels following a single dose are essentially identical to those following repeated administration. However, with levodopa/carbidopa controlled-release tablets, 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 2 half tablets of levodopa/carbidopa controlled-release formulation, 200 mg/ 50 mg, is approximately 20% greater than that of one intact tablet. The bioavailability of levodopa/carbidopa controlled-release tablets is somewhat increased in the presence of food. Dose-proportionality has been demonstrated over the dose range of one and two levodopa/ carbidopa controlled-release tablets, 200 mg/50 mg.

The pharmacokinetics of levodopa following administration of levodopa/carbidopa controlled-release tablets, 100 mg/25 mg were studied in patients with Parkinson's disease. Chronic three month, open-label, twice daily dosing with levodopa/carbidopa controlled-release tablets, 100 mg/25 mg (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 levodopa/carbidopa controlled-release tablet, 100 mg/25 mg, was equivalent to that for one levodopa/carbidopa controlled-release tablet, 200 mg/50 mg. The mean peak concentration of levodopa following the administration of one levodopa/carbidopa controlled-release tablet, 100 mg/25 mg, was greater than 50% of that following the administration of one levodopa/carbidopa controlled release tablet, 200 mg/50 mg. Mean time-to-peak plasma levels may be slightly less for levodopa/carbidopa controlled-release tablets, 100 mg/25 mg, than for levodopa/ carbidopa controlled-release tablets, 200 mg/50 mg.

STORAGE AND STABILITY

LEVOCARB CR (levodopa and carbidopa) Tablets should be stored at room temperature (15°-30°C). Protect from sunlight.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LEVOCARB CR 100 mg/25 mg: Each oval, pink, biconvex tablet engraved “100" over "25" on one side, contains 100 mg of levodopa and 25 mg of anhydrous carbidopa. Available in bottle of 100.

LEVOCARB CR 200 mg/50 mg: Each oval, peach, biconvex tablet scored and engraved “200" over "50" on one side, contains 200 mg of levodopa and 50 mg of anhydrous carbidopa. Available in bottle of 100.

LEVOCARB 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. In addition to levodopa and carbidopa, each tablet contains the non-medicinal ingredients: Hydroxypropyl Methylcellulose USP, Yellow Ferric Oxide (200 mg/50 mg tablets only), Red Ferric Oxide NF Orange Shade #34690, Purified Water USP, and Magnesium Stearate NF.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Levodopa and Carbidopa

Chemical Name:

Levodopa

1) L-Tyrosine,3-hydroxy-;
2) (-)-3-(3,4-Dihydroxyphenyl)-L-alanine.

Carbidopa

1) Benzenepropanoic acid,α-hydrazino-3,4-dihydroxy-α-methyl, monohydrate, (S);
2) (-)-L-α-Hydrazino-3,4-di-hydroxy-α-methylhydrocinnamic acid monohydrate.

Molecular formula and molecular weight:

Levodopa: $C_9H_{11}NO_4$, 197.19

Carbidopa: $C_{10}H_{14}N_2O_4.H_2O$, 244.25

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

Structural Formula:

Levodopa

Carbidopa

Physicochemical properties:	**Levodopa:** White to off white, odourless, crystalline powder. In the presence of moisture, is rapidly oxidized by atmospheric oxygen and darkens. Slightly soluble in water; freely soluble in 3N hydrochloric acid; insoluble in alcohol. **Carbidopa:** White to creamy white, odourless or practically odourless powder. Slightly soluble in water; freely soluble in 3N hydrochloric acid; slightly soluble in methanol; practically insoluble in alcohol, in acetone, in chloroform and in ether.

CLINICAL TRIALS

Three comparative bioavailability studies were performed, one under fasted, one under fed and one under steady-state conditions. The double-blind, randomized, two-way crossover studies were conducted in healthy, adult, male volunteers to evaluate the relative bioavailability of 1 x 50 mg/ 200 mg doses of LEVOCARB CR Tablet manufactured by AA Pharma Inc. and Sinemet® CR Tablet manufactured by Merck Sharp & Dohme, Canada. The mean pharmacokinetic parameters of these subjects are summarized in the following tables:

Fasting Study: Summary Table of the Comparative Bioavailability Data Carbidopa/Levodopa CR Tablets 50 mg/200 mg (1 x 50 mg/200 mg Tablet)			
Carbidopa:			
Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (%) (90% CI)**
	LEVOCARB CR	**SINEMET® CR†**	
AUC_T (ng•h/mL)	582.1 675.1 (50.9)	559.3 628.6 (46.6)	104.1 (0.94 - 1.16)
AUC_I (ng•h/mL)	602.8 693.5 (49.7)	578.7 646.6 (45.6)	104.2 (0.94 - 1.16)
C_{max} (ng/mL)	117.2 133.0 (45.4)	114.2 126.4 (44.0)	102.6
T_{max}^* (h)	3.985 (23.6)	3.515 (31.5)	--
$T_{½}^*$ (h)	2.353 (29.7)	2.355 (18.3)	--

* Arithmetic means (CV%);
† Sinemet® CR is manufactured by Merck Sharp & Dohme, Canada and was purchased in Canada.

Fasting Study: Summary Table of the Comparative Bioavailability Data Carbidopa/Levodopa CR Tablets 50 mg/200 mg (1 x 50 mg/200 mg Tablet)			
Levodopa:			
Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (%) (90% CI)**
	LEVOCARB CR	**SINEMET® CR†**	
AUC_T (ng•h/mL)	3448 3599 (29.9)	3601 3699 (23.9)	95.75 (0.90 - 1.01)
AUC_I (ng•h/mL)	3523 3674 (29.5)	3676 3773 (23.6)	95.84 (0.90 - 1.01)
C_{max} (ng/mL)	816.8 851.8 (30.0)	886.0 929.1 (32.7)	92.19
T_{max}^* (h)	2.561 (28.4)	2.167 (40.2)	--
$T_{½}^*$ (h)	1.577 (13.2)	1.597 (12.5)	--

* Arithmetic means (CV%);
† Sinemet® CR is manufactured by Merck Sharp & Dohme, Canada and was purchased in Canada.

Fed Study: Summary Table of the Comparative Bioavailability Data Carbidopa/Levodopa CR Tablets 50 mg/200 mg (1 x 50 mg/200 mg Tablet)			
Carbidopa:			
Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (%) (90% CI)**
	LEVOCARB CR	**SINEMET® CR†**	
AUC_T (ng•h/mL)	440.0 476.6 (44.8)	444.6 486.7 (44.0)	98.97 (0.91 - 1.07)
AUC_I (ng•h/mL)	455.4 491.3 (43.6)	459.1 500.2 (43.0)	99.19 (0.92 - 1.07)
C_{max} (ng/mL)	91.70 99.31 (42.1)	95.05 102.9 (41.9)	96.48
T_{max}* (h)	4.791 (23.6)	4.292 (26.2)	--
$T_{½}$* (h)	1.931 (18.0)	1.958 (14.1)	--

* Arithmetic means (CV%);
† Sinemet® CR is manufactured by Merck Sharp & Dohme, Canada and was purchased in Canada.

Fed Study: Summary Table of the Comparative Bioavailability Data Carbidopa/Levodopa CR Tablets 50 mg/200 mg (1 x 50 mg/200 mg Tablet)			
Levodopa:			
Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (%) (90% CI)**
	LEVOCARB CR	**SINEMET® CR†**	
AUC_T (ng•h/mL)	3524 3621 (24.9)	3562 3679 (26.3)	98.93 (0.97 - 1.02)
AUC_I (ng•h/mL)	3604 3699 (24.3)	3635 3752 (25.9)	99.15 (0.97 - 1.02)
C_{max} (ng/mL)	938.1 992.7 (35.5)	1106 1152 (29.0)	84.82
T_{max}* (h)	3.629 (25.4)	3.052 (28.2)	--
$T_{½}$* (h)	1.531 (11.6)	1.540 (11.6)	--

* Arithmetic means (CV%);
† Sinemet® CR is manufactured by Merck Sharp & Dohme, Canada and was purchased in Canada.

Steady-State Study: Summary Table of the Comparative Bioavailability Data Carbidopa/Levodopa CR Tablets 50 mg/200 mg (1 x 50 mg/200 mg Tablet)			
Carbidopa:			
Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (%) (90% CI)**
	LEVOCARB CR	**SINEMET® CR†**	
AUC_T (ng•h/mL)	598.3 648.95 (42.2)	630.3 687.37 (44.5)	94.92 (0.82 - 1.09)
C_{max} (ng/mL)	128.2 140.07 (45.2)	145.9 164.65 (50.7)	87.87 (0.74 - 1.04)
C_{min} (ng/mL)	23.85 27.96 (61.3)	23.76 27.65 (59.8)	100.38
T_{max}* (h)	3.360 (29.3)	3.446 (38.6)	--
FL* (%)	140.4 (29.7)	159.6 (39.1)	--

* Arithmetic means (CV%);
† Sinemet® CR is manufactured by Merck Sharp & Dohme, Canada and was purchased in Canada.

Steady-State Study: Summary Table of the Comparative Bioavailability Data Carbidopa/Levodopa CR Tablets 50 mg/200 mg (1 x 50 mg/200 mg Tablet)			
Levodopa:			
Parameter	**Geometric Mean Arithmetic Mean (CV %)**		**Ratio of Geometric Means (%) (90% CI)**
	LEVOCARB CR	**SINEMET® CR†**	
AUC_T (ng•h/mL)	4028 4156.36 (25.1)	4303 4403.72 (21.5)	93.61 (0.87 - 1.00)
C_{max} (ng/mL)	1064 1100.64 (27.9)	1176 1225.12 (29.3)	90.48 (0.83 - 0.99)
C_{min} (ng/mL)	94.65 108.96 (51.8)	89.56 100.67 (48.6)	105.68
T_{max}* (h)	2.082 (31.4)	1.564 (61.9)	--
FL* (%)	193.6 (19.2)	204.3 (22.0)	--

* Arithmetic means (CV%);
† Sinemet® CR is manufactured by Merck Sharp & Dohme, Canada and was purchased in Canada.

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 dihydroxy-mandelic 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, levo-dopa-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 ^{14}C 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 ^{14}C-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 percent 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

Acute Toxicity

Summary of Acute Oral Toxicity Data			
Species	**Sex**	**LD_{50} (mg/kg)**	**Signs of Toxicity**
A) CARBIDOPA			
Rat (A&W)	F	4810	
Rat (A&W)	M	5610	Ptosis, ataxia,
Rat (I)	M & F	2251	decreased activity.
Mouse (A)	F	1750	As above plus bradypnea.
B) LEVODOPA			
Rat (A)	F	2260	Vocalization, irritability, excitability, increased activity followed by decreased activity.
Rat (A)	M	1780	
Mouse	F	1460	
C) LEVODOPA/CARBIDOPA (1:1)			
Mouse	M & F	1930*	Erect tail, piloerection, ataxia, lacrimation, increased activity & irritability, clonic convulsion.
D) LEVODOPA/CARBIDOPA (3:1)			
Mouse	M & F	3270*	As above.

*Sum of individual doses of levodopa/carbidopa
A - Adult; W - Weanling; I - Infant

The preceding table summarizes the acute toxicity data for levodopa and carbidopa alone and in combination. Mortality usually occurred in 12 hours with carbidopa and 30 minutes with levodopa. With the combination of levodopa and carbidopa, 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 ptyalism, piloerection, hyperventilation with intermittent dyspnea and decreased activity.

Combinations of levodopa and carbidopa 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 levodopa and carbidopa 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 benztropine 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 10:1 mixture of levodopa:carbidopa 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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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

[Pr]LEVOCARB CR
Levodopa and Carbidopa Controlled-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when [Pr]LEVOCARB 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 [Pr]LEVOCARB CR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your physician has prescribed LEVOCARB 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:
LEVOCARB CR tablets are formulated to slowly release the two active ingredients, levodopa and carbidopa. LEVOCARB 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.

It is believed that the symptoms of Parkinson's disease are caused by a lack of dopamine, a naturally occuring 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 LEVOCARB CR:
- if you are allergic to carbidopa, levodopa any of the non-medicinal ingredients (see What the important nonmedicinal ingredients are)
- if you have any suspicious skin lesions (moles) which have not been examined by your doctor or if you have ever had skin cancer
- if you are been treated for depression with certain MAO inhibitor drugs
- if you have narrow-angle glaucoma

What the medicinal ingredient is:
LEVOCARB CR tablets contain the active ingredients carbidopa and levodopa.

What the important nonmedicinal ingredients are:
LEVOCARB CR contains the following non-medicinal ingredients: Hydroxypropyl Methylcellulose USP, Yellow Ferric Oxide NF (200 mg/50 mg tablets only), Red Ferric Oxide NF, Purified Water USP and Magnesium Stearate NF.

What dosage forms it comes in:
LEVOCARB CR controlled-release tablets are available in 100 mg/25 mg (levodopa/carbidopa) and 200 mg/50 mg (levodopa/carbidopa) strengths.

WARNINGS AND PRECAUTIONS

Before starting [Pr]LEVOCARB CR tell your doctor or pharmacist if:

- you have or have had any medical conditions including: allergies;
- depression or mental disturbances;
- lung, kidney, liver, heart or hormonal problems;
- peptic ulcer disease;
- convulsions;
- or glaucoma
- you have previously been treated with levodopa
- you are pregnant or nursing

It is not recommended to use LEVOCARB CR while you are pregnant or breast-feeding. Levodopa, one of the components of LEVOCARB 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 the possible hazards to your baby.

INTERACTIONS WITH THIS MEDICATION

Tell your physician about all medicines you are taking or plan to take, including those obtained without a prescription.

Drugs that may interact with LEVOCARB CR include:
- antihypertensive drugs (used to treat elevated blood pressure)
- psychoactive drugs (phenothiazines, butyrophenones and risperidone used in the treatment of depression)
- selegiline
- tricyclic antidepressants
- isoniazid
- iron salts
- metoclopramide
- drugs used to treat muscle spasms or convulsions

A change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation.

Excessive acidity delays stomach emptying, thus delaying the absorption of levodopa.

Iron salts (such as in multi-vitamin tablets) may also reduce the amount of levodopa available to the body.

The above factors may reduce the clinical effectiveness of the levodopa or levodopa/carbidopa therapy.

PROPER USE OF THIS MEDICATION

Usual dose:
The dosage of LEVOCARB CR is variable and your physician will adjust it according to the severity of your disease and your response to treatment.

LEVOCARB 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 LEVOCARB CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of LEVOCARB (levodopa/carbidopa). Consult your physician if such delayed responses pose a problem in treatment.

If so prescribed, the LEVOCARB CR 200 mg/50 mg tablets may be broken in half. The whole or half tablet should be swallowed without chewing or crushing in order to maintain the slow-release properties of LEVOCARB CR.

For best results take LEVOCARB CR every day. It is important to carefully follow your physician's advice on how much LEVOCARB 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.

LEVOCARB CR should not be given to children.

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

Missed Dose:
Try to take LEVOCARB 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

LEVOCARB CR is generally well tolerated. Like any other medicine, however, LEVOCARB CR may have unintended or undesirable effects, so called side-effects.

The most frequent side effects are:
- abnormal movements (which may or may not resemble your Parkinson's symptoms)
- nausea
- hallucinations,
- confusion
- dizziness
- dry mouth

Other possible side effects include:
- abnormal dreams or difficulty sleeping
- sleepiness, sudden sleep onset episodes
- mental changes
- depression
- weakness

- vomiting
- loss of appetite
- increased sexual drive
- flushing
- hair loss
- fainting.
- occasionally, dark color (red, brown or black) may appear in your saliva, urine or sweat after you take LEVOCARB CR.

Hypersensitivity reactions may occur such as hives, itching, rash, and swelling of the face, lips, tongue, and/or throat, which may cause difficulty in breathing or swallowing: contact your physician immediately if these symptoms occur.

LEVOCARB CR may affect some patients' ability to stay awake. If you feel drowsy or experience sudden onset of sleep, you should not drive or operate machinery.

This is not a complete list of side effects. For any unexpected effects while taking ^{Pr}LEVOCARB CR, contact your doctor or pharmacist.

HOW TO STORE IT

Store your tablets in a tightly closed container at room temperature (15° - 30°C). Protect from sunlight.

Remember – This medicine is prescribed for the particular condition that you have. Do not give this medicine to other people, not use it for any other condition.

Do not use outdated medicine.

Keep all medicines out of the reach of children.

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
    Address Locator: 0701D
    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.

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

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

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