

PRODUCT MONOGRAPH

PrTEVA-LEVOCARBIDOPA

(levodopa and carbidopa tablets, USP)

100 mg/10 mg
100 mg levodopa and 10 mg carbidopa

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

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

Antiparkinson Agent

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PrTEVA-LEVOCARBIDOPA

(levodopa and carbidopa tablets, USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	tablet 100 mg/10 mg, 100 mg/25 mg, 250 mg/25 mg	Microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch, FD&C Blue #2 Aluminum Lake (100/10 mg), D&C Yellow #6 Aluminum Lake, D&C Yellow #10 Aluminum Lake (100/25 mg), FD&C Blue #2 Aluminum Lake (250/25 mg).

INDICATIONS AND CLINICAL USE

TEVA-LEVOCARBIDOPA (levodopa and carbidopa) is indicated for the treatment of Parkinson's disease.

TEVA-LEVOCARBIDOPA is not recommended for the treatment of drug-induced extrapyramidal reactions.

Although the administration of carbidopa permits control of Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at lower dosages and sooner during therapy with TEVA-LEVOCARBIDOPA than with levodopa.

Pediatrics (< 18 years of age):

The safety and effectiveness of TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA (levodopa and carbidopa). These inhibitors must be discontinued at least two weeks prior to initiating therapy with TEVA-LEVOCARBIDOPA. TEVA-LEVOCARBIDOPA 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.
- TEVA-LEVOCARBIDOPA 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, TEVA-LEVOCARBIDOPA 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, TEVA-LEVOCARBIDOPA 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 levodopa and carbidopa tablets 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 levodopa and carbidopa tablets, 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 TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA. If drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician.

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

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

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

General

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

Patients who are taking TEVA-LEVOCARBIDOPA should be instructed not to take additional levodopa unless it is prescribed by the physician.

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy with TEVA-LEVOCARBIDOPA (levodopa and

carbidopa).

Physical Activity

Patients who improve while on therapy with TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA to patients with a history of myocardial infarction or who have atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment in a facility with provisions for intensive cardiac care.

Gastrointestinal

TEVA-LEVOCARBIDOPA should be administered cautiously to patients with a history of peptic ulcer disease due to the possibility of upper gastrointestinal hemorrhage.

Neurologic

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

As with levodopa, TEVA-LEVOCARBIDOPA may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. Because carbidopa permits more levodopa to reach the brain and thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with TEVA-LEVOCARBIDOPA than with levodopa. The occurrence of dyskinesias may require dosage reduction.

TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Psychomotor Performance

Certain side effects that have been reported with levodopa and carbidopa tablets 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 TEVA-LEVOCARBIDOPA. If

drowsiness or sudden onset of sleep should occur, patients should be informed to refrain from driving or operating machines and to immediately contact their physician (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Sudden Onset of Sleep).

Ophthalmologic

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

Peri-Operative Considerations

If general anesthesia is required, therapy with TEVA-LEVOCARBIDOPA may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication (see DOSAGE AND ADMINISTRATION, Adjustment and Maintenance of Therapy).

Psychiatric

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

Behavioural Changes

Patients and caregivers should be advised to adhere to dosage instructions given by the physician. Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioural 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 levodopa and carbidopa tablets (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 TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA 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. TEVA-LEVOCARBIDOPA should not be given to nursing mothers unless the anticipated benefits to the mother outweigh the potential hazards to the infant.

Pediatrics (< 18 years of age): The safety of TEVA-LEVOCARBIDOPA in patients under 18 years of age has not been established.

Monitoring and Laboratory Tests

Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy with TEVA-LEVOCARBIDOPA (levodopa and carbidopa).

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

ADVERSE REACTIONS

Clinical Trial and Post-Market Adverse Drug Reactions

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

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

Body as a whole:

Syncope, chest pain, anorexia, asthenia.

Cardiovascular:

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

Gastrointestinal:

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

Hematologic:

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

Hypersensitivity:

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

Musculoskeletal:

Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric:

Neuroleptic malignant syndrome (see WARNINGS AND PRECAUTIONS), bradykinetic episodes (the “on-off” phenomenon), dizziness, somnolence including very rarely excessive daytime somnolence and sudden sleep onset episodes, paresthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, dream abnormalities including nightmares, insomnia, headache, depression with or without development of suicidal tendencies, dementia, agitation, confusion.

In post-marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating have been reported with dopamine.

Respiratory:

Dyspnea, upper respiratory infection.

Skin:

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

Urogenital:

Dark urine, urinary frequency, urinary tract infection.

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

Body as a whole:

Fatigue.

Cardiovascular:

Myocardial infarction.

Gastrointestinal:

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

Metabolic:

Weight gain or loss, edema.

Musculoskeletal:

Leg pain.

Nervous System/Psychiatric:

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

Respiratory:

Pharyngeal pain, cough.

Skin:

Flushing.

Special Senses:

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

Urogenital:

Urinary retention, urinary incontinence, priapism.

Miscellaneous:

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

Abnormal Hematologic and Clinical Chemistry Findings

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

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

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

DRUG INTERACTIONS

Drug-Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with TEVA-LEVOCARBIDOPA:

Antihypertensive Drugs: Symptomatic postural hypotension can occur when TEVA-LEVOCARBIDOPA is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA should be carefully observed for loss of antiparkinsonian effect.

Concomitant therapy with selegiline and levodopa-carbidopa preparations may be associated with severe orthostatic hypotension not attributable to levodopa-carbidopa alone (see CONTRAINDICATIONS).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and levodopa and carbidopa tablets. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

Dopamine Depleting Agents: Use of TEVA-LEVOCARBIDOPA 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, TEVA-LEVOCARBIDOPA should be discontinued the night before. Therapy with TEVA-LEVOCARBIDOPA may be continued as soon as the patient is able to take medication by mouth.

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

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

Drug-Food Interactions

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

Drug-Laboratory Interactions

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

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

If a patient being treated with levodopa is switched to therapy with TEVA-LEVOCARBIDOPA, levodopa must be discontinued at least twelve hours or more before therapy with TEVA-LEVOCARBIDOPA is initiated.

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

The tablet score-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. If subdivided, the tablet should be consumed as a whole dose.

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

For patients who require only low doses of levodopa, e.g., less than 700 mg, TEVA-LEVOCARBIDOPA 100/25 may be helpful.

Recommended Dose and Dosage Adjustment

Induction of Therapy in Patients Not Receiving Levodopa

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

While increasing the dosage during the induction period, the doses should be divided, aiming at a frequency of dosing of at least four times a day. If further titration is necessary after a daily dosage level of six tablets of TEVA-LEVOCARBIDOPA 100/25 has been reached, tablets of TEVA-LEVOCARBIDOPA 100/10 or TEVA-LEVOCARBIDOPA 250/25 may be used as needed to provide the optimal dosage.

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

Induction of Therapy in Patient Receiving Levodopa

Levodopa must be discontinued at least twelve hours or more before TEVA-LEVOCARBIDOPA is started. A dosage of TEVA-LEVOCARBIDOPA should be used that will provide approximately 20% of the previous levodopa daily dosage; this can be started in the morning after the day in which the treatment with levodopa has been stopped. For example, if a patient is receiving 4,000 mg of levodopa per day, the dosage of TEVA-LEVOCARBIDOPA should not provide more than 750 mg of levodopa per day divided into four to six doses.

Tablets of TEVA-LEVOCARBIDOPA 100/25 should be used to start medication for patients requiring lower dosages of levodopa.

Adjustment and Maintenance of Therapy

Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, one tablet of TEVA-LEVOCARBIDOPA 100/25 may be substituted for each tablet of TEVA-LEVOCARBIDOPA 100/10. When more levodopa is required, TEVA-LEVOCARBIDOPA 250/25 should be substituted for TEVA-LEVOCARBIDOPA 100/25 or 100/10. If necessary, the dosage of TEVA-LEVOCARBIDOPA 250/25 may be increased by one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Because both therapeutic and adverse responses occur more rapidly with TEVA-LEVOCARBIDOPA than with levodopa alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with TEVA-LEVOCARBIDOPA than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Current evidence indicates that other standard antiparkinsonian drugs may be continued while TEVA-LEVOCARBIDOPA is being administered although their dosage may have to be adjusted.

If general anesthesia is required, therapy with TEVA-LEVOCARBIDOPA may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

Missed Dose

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre immediately.

Management of acute overdosage with TEVA-LEVOCARBIDOPA (levodopa and carbidopa) is basically the same as management of acute overdosage with levodopa alone. However, pyridoxine is not effective in reversing the actions of TEVA-LEVOCARBIDOPA.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the possible development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as TEVA-LEVOCARBIDOPA should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

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

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

Pharmacokinetics

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

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

The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours.

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

Pyridoxine hydrochloride (vitamin B₆), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

STORAGE AND STABILITY

Store bottles between 15-30°C, keep tightly closed and protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-LEVOCARBIDOPA (levodopa and carbidopa) is available as:

100 mg/10 mg: a mottled blue coloured, oval-shaped, single-scored compressed tablet, engraved '100/10' with scoreline on one side and 'NOVO' on the other side, containing 100 mg levodopa and 10 mg carbidopa.

100 mg/25 mg: a mottled yellow coloured, oval-shaped, single-scored compressed tablet, engraved '100/25' with scoreline on one side and 'NOVO' on the other side, containing 100 mg levodopa and 25 mg carbidopa.

250 mg/25 mg: a mottled blue coloured, oval-shaped, single-scored compressed tablet, engraved '250/25' with scoreline on one side and 'NOVO' on the other side containing 250 mg levodopa and 25 mg carbidopa.

Composition:

TEVA-LEVOCARBIDOPA 100/10 contains: FD&C Blue #2 Aluminum Lake, microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch.

TEVA-LEVOCARBIDOPA 100/25 contains: D&C Yellow #6 Aluminum Lake, D&C Yellow #10 Aluminum Lake, microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch.

TEVA-LEVOCARBIDOPA 250/25 contains: FD&C Blue #2 Aluminum Lake, microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch.

TEVA-LEVOCARBIDOPA is available in bottles of 100 and 500 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Levodopa and Carbidopa

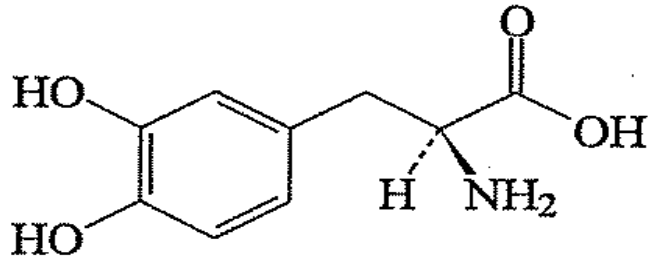
Levodopa:

Chemical name: (-)-3-(3,4-Dihydroxyphenyl)-L-alanine

Molecular formula: $C_9H_{11}NO_4$

Molecular mass: 197.19 g/mol

Structural formula:



Physicochemical properties: Levodopa is a fine, white to off-white, crystalline powder that is oxidized by atmospheric oxygen in the presence of moisture and darkness. Its solubility is 1 g in 10 mL 0.1N HCl, 250 mL water, 555 mL alcohol and 1000 mL chloroform. The pH of aqueous solution is between 4.5 and 7.0. The melting point is between 276-278°.

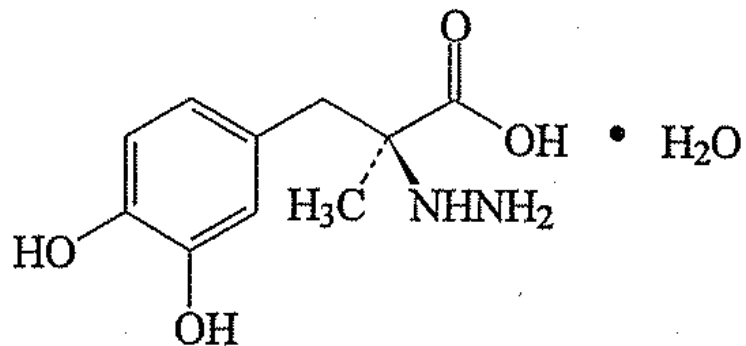
Carbidopa:

Chemical name: (-)-L- α -Hydrazino-3,4-dihydroxy- α -methylhydrocinnamic acid monohydrate

Molecular formula: $C_{10}H_{14}N_2O_4 \cdot H_2O$

Molecular mass: 244.25 g/mol

Structural formula:



Physicochemical properties: Carbidopa is a white to creamy white, odourless or practically odourless powder that is slightly soluble in water, practically insoluble in alcohol, chloroform and ether, and freely soluble in 3N hydrochloric acid. It has a pH of 4.7 and a melting point between 203-205°.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative, two-way single dose bioavailability study was performed on two levodopa/carbidopa 250 mg/25 mg tablets, TEVA-LEVOCARBIDOPA (levodopa and carbidopa) 250 mg/25 mg and Sinemet® 250 mg/25 mg tablets. The pharmacokinetic data calculated for levodopa and carbidopa in the TEVA-LEVOCARBIDOPA 250/25 and Sinemet® 250/25 tablet formulations is tabulated as follows:

Carbidopa:

Levocarbidoa (1 X 250 mg/25 mg) From measured data				
Geometric mean Arithmetic mean (CV%)				
Parameter	TEVA- LEVOCARBIDOPA 1 X 250 mg/25 mg	Sinemet® 1 x 250 mg/25 mg	% Ratio of Geometric Mean	90% Confidence Interval
AUC _T (ng·h/mL)	180.9 194.8 (40)	174.4 189.6 (43)	104	92.27 – 116.65%
AUC _I (ng·h/mL)	184.9 198.8 (39)	178.6 193.6 (42)	104	92.29 – 116.20%
C _{max} (ng/mL)	45.62 48.79 (39)	47.15 52.11 (48)	97	84.67 – 110.52%
T _{max} * (h)	2.41 (1.05)	2.35 (1.00)	-	-
t _{1/2} * (h)	1.66 (0.43)	1.70 (0.36)	-	-

* For the T_{max} and t_{1/2} parameter these are the arithmetic means (SD%).
 ** Sinemet® 250 Tablets (Merck, Sharpe & Dohme for DuPont Pharma, Canada).

Levodopa:

Levocarbido^a (1 X 250 mg/25 mg) From measured data				
Geometric mean Arithmetic mean (CV%)				
Parameter	TEVA- LEVOCARBIDOPA 1 X 250 mg/25 mg	Sinemet [®] 1 x 250 mg/25 mg	% Ratio of Geometric Mean	90% Confidence Interval
AUC _T (ng·h/mL)	4171 4231 (17)	4224 4281 (17)	99	94.90 – 102.74
AUC _I (ng·h/mL)	4193 4254 (17)	4246 4303 (17)	99	94.96 – 102.72
C _{max} (ng/mL)	1834 1944 (38)	1744 1816 (31)	105	95.37 – 115.92%
T _{max} [*] (h)	1.25 (0.81)	1.49 (0.88)	-	-
t _{1/2} [*] (h)	1.54 (0.18)	1.57 (0.24)	-	-

* For the T_{max} and t_{1/2} parameter these are the arithmetic means (SD%).
** Sinemet[®] 250 Tablets (Merck, Sharpe & Dohme for DuPont Pharma, Canada).

A second comparative, two-way single dose bioavailability study was performed on two levodopa/carbidopa 100 mg/25 mg tablets, TEVA-LEVOCARBIDOPA 100 mg/25 mg and Sinemet[®] 100 mg/25 mg. The pharmacokinetic data calculated from the study of TEVA-LEVOCARBIDOPA 100/25 and Sinemet[®] 100/25 is tabulated as follows:

Carbidopa:

Levocarbido^a (1 X 100 mg/25 mg) From measured data				
Geometric mean Arithmetic mean (CV%)				
Parameter	TEVA- LEVOCARBIDOPA 1 X 100 mg/25 mg	Sinemet [®] 1 x 100 mg/25 mg	% Ratio of Geometric Mean	90% Confidence Interval
AUC _T (ng·h/mL)	223.3 242.7 (39)	219.9 238.9 (40)	102	91.34 – 112.91%
AUC _I (ng·h/mL)	227.3 246.4 (38)	223.9 242.7 (39)	102	91.46 – 112.67%
C _{max} (ng/mL)	61.88 68.05 (44)	59.90 65.26 (40)	103	91.30 – 116.92%
T _{max} [*] (h)	2.21 (0.93)	2.11 (0.90)	-	-
t _{1/2} [*] (h)	1.80 (0.30)	1.86 (0.39)	-	-

* For the T_{max} and t_{1/2} parameter these are the arithmetic means (SD%).
** Sinemet[®] 100/25 Tablets (Merck, Sharpe & Dohme for DuPont Pharma, Canada).

Levodopa:

Levocarbido^a (1 X 100 mg/25 mg) From measured data				
Geometric mean Arithmetic mean (CV%)				
Parameter	TEVA- LEVOCARBIDOPA 1 X 100 mg/25 mg	Sinemet [®] 1 x 100 mg/25 mg	% Ratio of Geometric Mean	90% Confidence Interval
AUC _T (ng·h/mL)	1463 1487 (19)	1484 1509 (18)	99	95.05 – 102.19%
AUC _I (ng·h/mL)	1481 1505 (18)	1503 1527 (18)	99	95.07 – 102.09%
C _{max} (ng/mL)	893.4 947.9 (36)	833.8 894.5 (40)	107	97.07 – 118.27%
T _{max} [*] (h)	0.75 (0.58)	0.72 (0.43)	-	-
t _{1/2} [*] (h)	1.78 (0.15)	1.74 (0.13)	-	-

* For the T_{max} and t_{1/2} parameter these are the arithmetic means (SD%).
 ** Sinemet[®] 100/25 Tablets (Merck, Sharpe & Dohme for DuPont Pharma, Canada).

In a third comparative, two-way single dose bioavailability study, two levodopa/carbidopa 100 mg/10 mg tablets, TEVA-LEVOCARBIDOPA 100 mg/10 mg and Sinemet[®] 100 mg/10 mg were tested in fed volunteers. The pharmacokinetic data calculated from the study of TEVA-LEVOCARBIDOPA 100/10 and Sinemet[®] 100/10 in fed volunteers is tabulated as follows:

Carbidopa:

Levocarbido^a (3 X 100 mg/10 mg) From measured data				
Geometric mean Arithmetic mean (CV%)				
Parameter	TEVA- LEVOCARBIDOPA 3 X 100 mg/10 mg	Sinemet [®] 3 x 100 mg/10 mg	% Ratio of Geometric Mean	90% Confidence Interval
AUC _T (ng·h/mL)	34.67 40.48 (53)	37.95 42.03 (41)	91	81 – 102%
AUC _I (ng·h/mL)	29.36 44.70 (50)	43.01 46.52 (37)	90	82 – 99%
C _{max} (ng/mL)	10.96 12.53 (52)	11.88 12.80 (36.06)	92	82 – 103%
T _{max} [*] (h)	2.00 (0.84)	2.00 (0.80)	-	-
t _{1/2} [*] (h)	1.64 (18)	1.67 (24)	-	-

* For the T_{max} and t_{1/2} parameter these are the arithmetic means (SD%).
 ** Sinemet[®] 100/10 Tablets (Merck, Sharpe & Dohme for DuPont Pharma, Canada).

Levodopa:

Levocarbido^a (3 X 100 mg/10 mg) From measured data				
Geometric mean Arithmetic mean (CV%)				
Parameter	TEVA- LEVOCARBIDOPA 3 X 100 mg/10 mg	Sinemet[®] 3 x 100 mg/10 mg	% Ratio of Geometric Mean	90% Confidence Interval
AUC _T (ng·h/mL)	3375 3877 (23)	3850 3939 (23)	98	84 – 102%
AUC _I (ng·h/mL)	3801 3902 (23)	3876 3965 (22)	98	94 – 102%
C _{max} (ng/mL)	1362 1409 (28)	1411 1458 (27)	96	90 – 104%
T _{max} [*] (h)	1.75 (0.90)	1.50 (1.0)	-	-
t _{1/2} [*] (h)	1.49 (11)	1.48 (13)	-	-

* For the T_{max} and t_{1/2} parameter these are the arithmetic means (SD%).
 ** Sinemet[®] 100/10 Tablets (Merck, Sharpe & Dohme for DuPont Pharma, 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 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
Rat (A)	M	1780	
Mouse	F	1460	

			activity.
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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 TEVA-LEVOCARBIDOPA
(levodopa and carbidopa tablets, USP)**

This leaflet is part III of a three-part "Product Monograph" published when TEVA-LEVOCARBIDOPA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-LEVOCARBIDOPA. 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

TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA 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:

TEVA-LEVOCARBIDOPA is a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor. It treats the symptoms of Parkinson's disease.

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

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

When it should not be used:

Do not take TEVA-LEVOCARBIDOPA, if you:

- are allergic to any of its ingredients;
- have any suspicious skin lesions (moles) which have not been examined by your physician or if you have ever had skin cancer;

- are being treated with certain MAO inhibitor drugs, such as for depression, within the last 2 weeks;
- have narrow-angle glaucoma;
- have untreated heart, liver, kidney, lung, blood or hormonal disease;
- have been told that you should not take sympathomimetic drugs such as isoproterenol, amphetamines, epinephrine or cough and cold medications containing drugs related to epinephrine.

What the medicinal ingredients are:

Levodopa and carbidopa

What the non-medicinal ingredients are:

TEVA-LEVOCARBIDOPA 100/25 mg (levodopa, carbidopa) tablets: Each tablet contains 100 mg levodopa and 25 mg carbidopa as the active ingredients and the following non-medicinal ingredients: D&C Yellow #6 Aluminum Lake, D&C Yellow #10 Aluminum Lake, microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch.

TEVA-LEVOCARBIDOPA 100/10 mg (levodopa, carbidopa) tablets: Each tablet contains 100 mg levodopa and 10 mg carbidopa as the active ingredients and the following non-medicinal ingredients: FD&C Blue #2 Aluminum Lake, microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch.

TEVA-LEVOCARBIDOPA 250/25 mg (levodopa, carbidopa) tablets: Each tablet contains 250 mg levodopa and 25 mg carbidopa as the active ingredients and the following non-medicinal ingredients: FD&C Blue #2 Aluminum Lake, microcrystalline cellulose, magnesium stearate, starch, pregelatinized starch.

What dosage forms it comes in:

TEVA-LEVOCARBIDOPA is supplied as a tablet. TEVA-LEVOCARBIDOPA 100/25 mg (levodopa, carbidopa) is a mottled yellow coloured, oval-shaped, single-scored compressed tablet, engraved '100/25' with scoreline on one side and 'NOVO' on the other side.

TEVA-LEVOCARBIDOPA 100/10 mg (levodopa, carbidopa) is a mottled blue coloured, oval-shaped, single-scored compressed tablet, engraved '100/10' with scoreline on one side and 'NOVO' on the other side.

TEVA-LEVOCARBIDOPA 250/25 mg (levodopa, carbidopa) is a mottled blue coloured, oval-shaped, single-scored compressed tablet, engraved '250/25' with scoreline on one side and 'NOVO' on the other side.

IMPORTANT: PLEASE READ

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 TEVA-LEVOCARBIDOPA. During treatment with TEVA-LEVOCARBIDOPA 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 TEVA-LEVOCARBIDOPA should have periodic skin examinations.

BEFORE taking TEVA-LEVOCARBIDOPA, 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 TEVA-LEVOCARBIDOPA while you are pregnant or breastfeeding.

It is not known what effect TEVA-LEVOCARBIDOPA may have on human pregnancy. Levodopa, one of the components of TEVA-LEVOCARBIDOPA, 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 TEVA-LEVOCARBIDOPA, you may increase your

physical activity gradually and with caution related to any other medical conditions you may have.

TEVA-LEVOCARBIDOPA should not be given to children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Although TEVA-LEVOCARBIDOPA 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 (medication used to treat conditions related to involuntary movements such as Huntington's Disease);
- phenytoin (anti-epileptic medication);
- papaverine (medication for intestinal spasms);
- isoniazid (medication to treat tuberculosis);
- metoclopramide (for nausea and vomiting);
- iron salts (such as multivitamins tablets) which may reduce the amount of carbidopa and/or levodopa available to the body.

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

PROPER USE OF THIS MEDICATION

Usual dose:

The dosage of TEVA-LEVOCARBIDOPA is variable and your physician will adjust it according to the severity of your disease and your response to treatment.

The score-line on the tablets is not for dividing the tablets into smaller doses and should not be used that way. If you must divide a tablet to help you swallow it, make sure you have all of the tablet pieces (the full dose).

TEVA-LEVOCARBIDOPA is an immediate-release formulation of levodopa-carbidopa that is designed to begin release of ingredients within 30 minutes. For best results, take TEVA-LEVOCARBIDOPA every day. It is important to carefully follow your physician's advice on

IMPORTANT: PLEASE READ

how much TEVA-LEVOCARBIDOPA 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:

If you think you, or a person you are caring for, have taken too much TEVA-LEVOCARBIDOPA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Try to take TEVA-LEVOCARBIDOPA 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

TEVA-LEVOCARBIDOPA is generally well tolerated. Like any other medicine, however, TEVA-LEVOCARBIDOPA 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 levodopa and carbidopa tablets may affect some patients' ability to drive or operate machinery.

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

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

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

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

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

IMPORTANT: PLEASE READ

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Uneven (irregular) heart beat or palpitations.		✓	
Feeling of lightheaded-ness as when standing quickly.		✓	

This is not a complete list of side effects. For any unexpected effects while taking TEVA-LEVOCARBIDOPA, contact your doctor or pharmacist.

HOW TO STORE IT

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

Keep all medicines out of the reach of children.

Do not use outdated medicine.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

If you want more information about TEVA-LEVOCARBIDOPA:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer’s website <http://www.tevacanada.com>; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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