LEVODOPA (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾CN500

Commonly used brand name(s):Larodopa.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antidyskinetic.

Indications

General considerations

Although levodopa is the most effective 9, 11, 41, 44, 46, 48 antiparkinsonian medication and remains a mainstay of therapy for symptomatic treatment of Parkinson's disease, complications to long-term levodopa therapy appear commonly 48.

The majority of patients receiving chronic levodopa therapy experience serious adverse effects 48 , including motor fluctuations 3, 40, 47 , dyskinesias 11, 40, 43, 46 , and neuropsychiatric effects 3, 11, 47, 48.

Fluctuations in response to levodopa therapy represent a significant problem in the long-term management of patients with Parkinson's disease 40, 47.

Later stage motor complications are related to the severity and duration of the underlying disease, as well as to treatment-related factors such as the duration and dose of levodopa therapy 3, 39.

Patients who develop response fluctuations to levodopa therapy appear to lack the capacity to buffer fluctuations in plasma levels of levodopa 48.

One theory to explain the mechanism of fluctuation is that chronic, sporadic stimulation of striatal postsynaptic dopaminergic receptors from exogenous levodopa administration results in changes downstream from the nigrostriatal dopamine system 45, 48 ; residual dopaminergic neurons, attempting to compensate for loss of degenerated neurons, accelerate dopamine formation and rapidly release it, rather than retaining it in storage vesicles 45.

In addition, nondopaminergic neurons and other cells that possess significant decarboxylase activity become increasingly important sources of intrasynaptic dopamine 45.

Once synthesized in these cells, dopamine is immediately released 45 , resulting in intrasynaptic dopamine concentrations that reflect the marked swings in levodopa availability 45 and in the ensuing motor fluctuations.

Therapeutic response to levodopa therapy includes a short-duration response, in which improvement in motor disability lasts for a few hours after the administration of a single dose of levodopa, and a long-duration response, in which antiparkinsonian effects may last for many hours or days following discontinuation of levodopa. 46, 58

Controversies exist regarding the optimal time to initiate therapy with levodopa 48 and the optimal use of other antiparkinsonian medications throughout the disease process 48.

Accepted

Parkinsonism (treatment)¾Levodopa is indicated to alleviate symptoms and allow more normal body movements with improved muscle control in the treatment of idiopathic Parkinson's disease, postencephalitic parkinsonism, or symptomatic parkinsonism that may follow injury to the nervous system by carbon monoxide intoxication or manganese intoxication. It is also indicated in parkinsonism associated with cerebral arteriosclerosis. 1, 15, 31

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Chemical group¾Levorotatory isomer of dihydroxyphenylalanine (L-DOPA) 31 , which is the metabolic precursor of dopamine. 9, 31

Molecular weight¾197.19 10, 31

Solubility¾The solubility of levodopa in water is 66 mg in 40 mL. 50

Other properties¾In the presence of moisture, levodopa is oxidized by atmospheric oxygen and darkens. 50

Mechanism of action/Effect:

Normal motor function depends on the synthesis and release of dopamine by neurons projecting from substantia nigra to corpus striatum. The progressive degeneration of these neurons 41, 43, 45 that occurs in Parkinson's disease disrupts the nigrostriatal pathway 42 and results in diminished levels of the intrasynaptic neurotransmitter dopamine 43, 45.

Striatal dopamine levels in symptomatic Parkinson's disease are decreased by 60 to 80% 3, 43.

Striatal dopaminergic neurotransmission may be enhanced by exogenous supplementation of dopamine through administration of dopamine's precursor, levodopa. A small percentage of each levodopa dose crosses the blood-brain barrier and is decarboxylated to dopamine 9.

This newly formed dopamine then is available to stimulate dopaminergic receptors 9 , thus compensating for the depleted supply of endogenous dopamine 41.

Other actions/effects:

Levodopa's metabolite, dopamine, stimulates beta-adrenergic cardiac receptors 20 , interacts with the chemoreceptor zone in the area postrema, located outside the blood-brain barrier 42 , and promotes release of pituitary growth hormone 57.

Absorption:

Levodopa is rapidly absorbed from the proximal small intestine by the large neutral amino acid (LNAA) transport carrier system 34, 42.

This transport system is a saturable, sodium-independent, facilitated mechanism for aromatic and branched chain amino acids 34.

The capacity of the transport system is limited 34 , and levodopa must compete for energy-dependent proximal small bowel absorption sites 3, 46.

Stomach and intestinal walls contain abundant levels of the L-aromatic amino acid decarboxylase (AAAD) enzyme, which degrades levodopa and thus serves as a significant barrier to the absorption of intact levodopa 34, 46 ; only about 30% of an orally administered dose reaches the circulation as intact levodopa 34.

Absorption may be enhanced by comcomitant administration of a peripheral decarboxylase inhibitor, such as carbidopa 3, 9, 46 or a catechol- O-methyltransferase (COMT) inhibitor, such as tolcapone 59, 60.

With long-term administration, levodopa absorption appears to become more efficient and complete 46.

High gastric acidity, delayed stomach emptying time, and the presence of certain other amino acids, such as those that occur after digestion of a protein-containing meal, may prevent absorption of levodopa. 3, 9, 34, 42, 46 Intense exercise and other activity that diverts blood flow from the mesenteric circulation also may delay levodopa absorption. 3, 34

Liquid formulations of levodopa have been extemporaneously compounded in an attempt to minimize absorption problems. The liquid preparation is absorbed slightly faster than levodopa tablets 44 , and antiparkinsonian effects may take effect more quickly than with levodopa tablets. Thus, the liquid preparation may be useful in patients who are extremely sensitive to small changes in the dose of levodopa, such as those experiencing erratic motor control 48 (e.g., severe oscillations between "on" and "off" periods 42). (See Side/Adverse Effects section and Preparation of dosage form section.)
Distribution:

Levodopa is widely distributed to most body tissues, but not to the central nervous system (CNS) because of extensive metabolism in the periphery 20.

Levodopa crosses biological membranes, including the intestinal epithelium and the blood-brain barrier, by means of the LNAA transport system. 3, 9, 34, 42, 46 This system is the saturable, stereospecific, facilitated transport mechanism for large neutral amino acids, including those from dietary protein intake 3, 9, 34, 41, 46.

The transport rate across the blood-brain barrier is dependent upon the plasma concentration of levodopa and the concentration of competing amino acids. 3 The flux of amino acids across the blood-brain barrier is bidirectional; the net flux of unmetabolized levodopa is from the brain into the plasma as levodopa plasma concentrations fall. 34

Biotransformation:

95% 46 of an administered oral dose of levodopa is pre-systemically 36 decarboxylated to dopamine by the L-aromatic amino acid decarboxylase (AAAD) enzyme 46 in the stomach, lumen of the intestine, kidney, and liver 3.

This converted portion of dopamine cannot cross the blood-brain barrier to exert its effects on the brain. 3 Dopamine remaining in the periphery is believed responsible for many levodopa adverse effects, including cardiac arrhythmias and gastrointestinal upset. 9, 34.

Levodopa also may be methoxylated 40 by the hepatic catechol- O-methyltransferase (COMT) enzyme system to 3- O-methyldopa (3-OMD), which cannot be converted to central dopamine 3.

3-OMD has a long half-life 3 and competes with levodopa for the same transport mechanism across the blood-brain barrier 3, 40.

When the portion of the remaining intact levodopa does cross the blood-brain barrier, it is decarboxylated to dopamine, which is normally stored in presynaptic terminals of dopaminergic neurons in the striatum 9, 36.

After release into the synapse, dopamine is transported back into the dopaminergic terminals by the presynaptic uptake mechanism, or is further metabolized by monoamine oxidase (MAO) or COMT 9.

The effects of levodopa in the brain are affected by the rate and extent of cerebral conversion to dopamine, the rate of movement of the synthesized dopamine to the striatal receptors, and the rate of inactivation of newly synthesized dopamine. 3

Half-life:

Levodopa: 0.75 to 1.5 hours. 11, 34, 44, 46

3-O-methyldopa (3-OMD): 15 hours; accumulation will occur during chronic dosing. 34

Onset of action:

Significant improvement may occur in 2 to 3 weeks. Some patients may require up to 6 months of continuous levodopa therapy to obtain optimal therapeutic benefit. 1, 31

Time to peak concentration:

0.5 to 2 hours 3, 9, 11, 46.

Elimination:

Renal, 70 to 80% of dose eliminated within 24 hours, largely as dopamine metabolites. 34 Homovanillic acid (HVA) is a major urinary metabolite, accounting for 13 to 42% of the ingested dose of levodopa in twenty-four hour urine samples. 31 Unchanged levodopa accounts for less than 1% of an administered dose. 9 Some of the eliminated metabolites may color the urine red 20 ; oxidation that occurs when urine is exposed to air will cause it to darken 20, 50.

Fecal, 2% of dose. 34

Precautions to Consider

Pregnancy/Reproduction

Pregnancy¾Adequate and well-controlled studies in humans have not been done. 15, 31 However, case studies have reported that levodopa crosses the placenta and is metabolized in the fetal tissues. 32

Reproduction studies in rodents have shown that levodopa, when given in doses in excess of 200 mg per kg of body weight (mg/kg) per day 1 , depresses fetal and postnatal growth and viability. 15, 31

Breast-feeding

Levodopa is distributed into breast milk. Although problems in humans have not been documented, breast-feeding is not recommended because of the potential for side effects in the infant. 15, 31

Also, levodopa may inhibit lactation. 59, 61

Pediatrics

Appropriate studies on the relationship of age to the effects of levodopa have not been performed in children up to 12 years of age. 1, 15 Safety and efficacy have not been established. 15, 31

Geriatrics

Smaller doses may be required in geriatric patients since they may have a reduced tolerance to the effects of levodopa 11.

Similarly, patients with Alzheimer's disease are more sensitive to usual doses of levodopa 11.

Geriatric patients, especially those with osteoporosis, who respond to levodopa therapy should resume normal activity gradually and with caution because increased mobility may increase risk of fractures. 16

Central nervous system (CNS) effects, such as anxiety, confusion, or nervousness, occur more frequently in geriatric patients receiving anticholinergic antiparkinsonian medications in addition to levodopa. 3

Geriatric patients, especially those with pre-existing coronary disease, are more susceptible to levodopa's cardiac effects, such as arrhythmias. These cardiac effects are minimized or eliminated when levodopa is combined with carbidopa. 13

Dental

Involuntary movements of jaws may result in poor retention of full dentures; dosage reduction may be required. 13

Surgical

If general anesthesia is required and the administration of levodopa is interrupted temporarily, the patient should be observed for symptoms of a neuroleptic malignant-like syndrome 32.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Amantadine 24, 46 or

Benztropine 21 or

Procyclidine 22 or

Trihexyphenidyl 23

(concurrent use may result in increased efficacy of levodopa; however, concurrent use is not recommended if there is a history of psychosis 3)

>> Anesthetics, hydrocarbon inhalation 14

(concurrent administration may result in cardiac arrhythmias because of increased endogenous dopamine concentration; levodopa should be discontinued 6 to 8 hours before administration of anesthetics, especially halothane)

Benzodiazepines 29, 37

(concurrent use may decrease the therapeutic effects of levodopa)

Bromocriptine 3

(may produce additive effects, allowing reduction in levodopa dosage)

>> Cocaine 8, 9

(concurrent use with levodopa may increase the risk of cardiac arrhythmias; if use of cocaine is necessary in patients receiving levodopa, it is recommended that cocaine be administered with caution, in reduced dosage, and in conjunction with electrocardiographic monitoring)

Droperidol 30 or

>> Haloperidol 27, 28 or

Loxapine 28 or

Molindone or

Papaverine 37 or

>> Phenothiazines 25, 26 or

>> Thioxanthenes 27

(agents that block the dopamine receptors in the brain, such as traditional antipyschotic agents, may antagonize the effects of levodopa)

Foods, especially high-protein 46, 48

(concurrent or previous ingestion of food may decrease the absorption of levodopa from the gastrointestinal tract, consequently delaying its effect; in addition, proteins in food may be degraded into amino acids that compete with levodopa for transport across the intestinal epithelium and the blood-brain barrier, resulting in a decreased or erratic response to levodopa; however, rather than cutting down on daily protein intake to avoid this effect, it has been recommended that the intake of proteins be distributed equally throughout the day; alternatively, some clinicians recommend a redistribution diet 48 for some patients for a limited time during which all protein intake is in the evening meal, as patients would be minimally affected by any ensuing "off" periods (see Side/Adverse Effects); diets with austere restrictions in total daily protein intake (£ 10 grams) have been shown to reduce the magnitude of response fluctuations and may benefit some patients, but are often unpalatable and may result in a negative nitrogen balance if not carefully monitored 46 ; a recommended dietary allowance of 0.8 gram of protein per kg of body weight a day is thought to be a sufficient and safe restriction that does not affect the levodopa dosage-response relationship 44)

Hypotension-producing medications, other 15, 16, 31 (see Appendix II)

(concurrent use with levodopa may result in an increased hypotensive effect)

Iron salts 32, 37 or

Vitamin/mineral preparations containing iron salts 32

(iron salts may chelate with levodopa, resulting in decreased absorption and lower serum levels of levodopa, and thus reduce its efficacy)

Methyldopa 16

(concurrent use with levodopa may alter the antiparkinsonian effects of levodopa and may also produce additive toxic CNS effects such as psychosis)

Metoclopramide 19, 33, 37

(metoclopramide may worsen Parkinson's disease through inhibition of CNS dopamine receptors; conversely, levodopa may antagonize the effects of metoclopramide by increasing the amount of available dopamine)

>> Monoamine oxidase (MAO) inhibitors 9, 15, 16, 31 , including furazolidone, procarbazine, and selegiline

(concurrent use with levodopa is not recommended as the combination may result in a hypertensive crisis; it is recommended that MAO inhibitors be discontinued for at least 2 weeks prior to initiation of levodopa therapy)

>> Pyridoxine (vitamin B 6) 9, 15, 16, 31, 34, 37, 46 or

>> Vitamin preparations containing pyridoxine 31, 46

(pyridoxine is a cofactor for dopa-decarboxylase, the enzyme responsible for the decarboxylation of levodopa; peripheral metabolism of levodopa is enhanced in the presence of pyridoxine, which results in decreased concentrations of levodopa available to compete for transport across the blood-brain barrier; concurrent use with levodopa is not recommended)

Rauwolfia alkaloids 16

(rauwolfia alkaloids cause dopamine depletion in the brain, decreasing the effects of levodopa; dosage adjustments of either or both medications may be necessary)

>> Selegiline 17, 18 or

Tolcapone 59, 60

(although sometimes used in conjunction with levodopa or with carbidopa and levodopa combination, selegiline or tolcapone may have additive effects; selegiline may enhance levodopa-induced dyskinesias, nausea, orthostatic hypotension, confusion, and hallucinations; levodopa dosage should be reduced within 2 to 3 days after the initiation of therapy with selegiline or tolcapone)

Sympathomimetic agents 9, 16

(concurrent use with levodopa may increase the possibility of cardiac arrhythmias, especially in patients with pre-existing conduction disturbances; dosage reduction of the sympathomimetic agent is recommended; the administration of carbidopa with levodopa reduces the tendency of sympathomimetic agents to cause dopamine-induced cardiac arrhythmias)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Catecholamines, urine 52 or

Metanephrines 52

(test results are unreliable)

Coombs' (antiglobulin) test 15, 31

(occasionally becomes positive after long-term levodopa therapy)

Glucose, urine

(tests using copper reduction methods may cause false-positive results; tests using glucose oxidase methods may cause false-negative results 54, 55, 56)

Gonadorelin test

(levodopa may elevate serum gonadotropin concentrations 53)

Ketones, urine

(tests using dipstick methods may cause false-positive results 52)

Protein, urine

(use of the Lowery test may cause false-positive results)

Thyroid function determinations

(chronic use of levodopa may inhibit the TSH response to protirelin 51)

Uric acid, serum and urine

(tests may show high concentrations with colorimetric measurements, but not with uricase 15, 31)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 15, 31 and

Alkaline phosphatase 15, 31 and

Aspartate aminotransferase (AST [SGOT]) 15, 31 and

Bilirubin 15, 31 and

Lactate dehydrogenase (LDH) 15, 31 and

Protein-bound iodine (PBI) 15, 31

(serum concentrations may be increased)

Blood urea nitrogen (BUN) 15, 31

(concentrations may be increased)

Hematocrit 31 and

Hemoglobin 31 and

White blood cell counts 31

(values may be decreased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Bronchial asthma, emphysema, and other severe pulmonary diseases 15, 16, 31

(respiratory effects of levodopa may aggravate condition)

>> Cardiovascular disease, severe 15, 16, 31

(increased risk of cardiac arrhythmias)

Convulsive disorders, history of 16

(use of levodopa may precipitate seizures)

Diabetes mellitus 16

(use of levodopa may adversely affect control of glucose in blood)

Endocrine diseases 15, 16, 31

(use of levodopa may adversely affect hypothalamus or pituitary function)

>> Glaucoma, angle-closure, or predisposition to 15, 31

(mydriatic effect resulting in increased intraocular pressure may precipitate an acute attack of angle-closure glaucoma)

Glaucoma, open-angle, chronic 15, 31

(mydriatic effect may cause a slight increase in intraocular pressure; glaucoma therapy may need to be adjusted 1)

Hepatic function impairment 15, 16, 31

>> Melanoma, history of or suspected 15

(use of levodopa may activate a malignant melanoma 32)

>> Mental depression 31 or

>> Psychosis 31

(increased risk of developing suicidal ideation and/or tendencies; also, conditions may be aggravated by neuropsychiatric effects of levodopa)

>> Myocardial infarction, history of, with residual atrial, nodal, or ventricular arrhythmias 15, 16, 31

(use of levodopa may precipitate or aggravate condition)

>> Peptic ulcer, history of 15, 31

(increased risk of upper gastrointestinal hemorrhage)

>> Renal function impairment 15, 16, 31

(use of levodopa may lead to urinary retention)

Sensitivity to levodopa 15, 31

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Blood cell counts 15, 16, 31 and

Hemoglobin determinations 15, 16, 31 and

Hepatic function determinations 15, 16, 31 and

Ophthalmologic examinations for glaucoma and monitoring of intraocular pressure in patients with open-angle glaucoma 31 and

Renal function determinations 15, 16, 31

(recommended at periodic intervals for patients on long-term levodopa therapy)

Cardiovascular monitoring 15, 16, 31

(recommended at periodic intervals for patients on long-term therapy)

Side/Adverse Effects

Note: A syndrome resembling neuroleptic malignant syndrome, which includes intermittent dystonia alternating with substantial agitation, hyperthermia, and mental changes, has been reported after the abrupt 12, 13 discontinuation of levodopa therapy. 5

Although levodopa is the most effective antiparkinsonian medication to date 9, 11, 41, 44, 46, 48 , complications to long-term levodopa therapy appear commonly and include motor fluctutations, dyskinesias, and neuropsychiatric problems 11, 39, 48.

Fifty percent or more of patients who have received levodopa for 5 years experience motor fluctuations 3, 39, 45, 46 ; after 10 years or more of treatment, up to 90% of patients may be affected 39, 46, 48.

Periods of therapeutic response in terms of antiparkinsonian effects are termed "on" periods 46, 48 ; "off" periods are periods of suboptimal response where the patient experiences a worsening of parkinsonian symptoms 48.

Motor fluctuations include predictable "wearing off" periods 43 , unpredictable "off" periods 43 , and various abnormal involuntary movements 39.

End-of-dose deterioration 45, 46 or "wearing off" periods 43 (predictable periods of immobility or greater severity of other parkinsonian symptoms when medications wear off 39) usually have a close temporal relationship to the timing of antiparkinsonian medication 39.

"On-off" fluctuations are sudden unpredictable shifts between "on" and "off" periods that are unrelated to the timing of antiparkinsonian medication 39, 43 ; relatively small changes in circulating levodopa, and thus in striatal dopamine, can induce large shifts in dopaminergic transmission and ultimately in motor function 43, 45.

Dyskinesias may include peak-dose (or square-wave) dyskinesias 43, 46, 47 (appearing during maximum effect), biphasic dyskinesias (appearing at beginning and end of dosing period) 11, 46, 47 , and focal or generalized dystonia 40, 47.

The severity of dyskinesias increases with time, as dyskinesias generally spread to a wider distribution of, and increase the degree of, abnormal movements 3.

Dyskinesias are dose-dependent, and the dose threshold decreases as Parkinson's disease progresses 42.

Random oscillations 40 include transient episodes of "freezing" or motor blocks 47 , where initiation or continuation of a motor act such as walking is arrested for a few seconds 39.

Yo-yoing is unpredictable 47 oscillations between choreic dyskinesia and Parkinsonian rigidity; patients may progress from severe dyskinesias to rigidity, or have an acceptable response to medication for part of the day ("ons") and be intermittently disabled by periods of suboptimal response ("offs") or dyskinesias 11.

Neuropsychiatric effects 3, 11, 48 may occur in up to two-thirds of patients on long-term levodopa therapy 47 and may be related to the activation of dopamine receptors in nonstriatal regions of the brain, especially the cortical and limbic regions 11, 42.

These mental and behavioral changes include confusion, agitation, hallucinations, irritability, panic, paranoid delusions, mental depression, dementia, mania, and psychosis 3, 11, 47, 48 ; euphoria, hypersexuality, or hypomania may occur during "on" periods 47.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Agitation 31, 42; anxiety 15, 16, 31; ataxia 31 (clumsiness or unsteadiness); bruxism 31 (clenching or grinding of teeth); choreiform and/or dystonic movements 15, 16, 31, 42 (unusual and uncontrolled movements of the body, including the face, tongue, arms, hands, head, and upper body); confusion 15, 16, 31; delusions 31 (abnormal thinking: holding false beliefs that cannot be changed by fact); dizziness 31; dysphagia 31, 48 (difficulty swallowing)¾may occur in up to 40% of patients 48; euphoria 31 (false sense of well-being); fatigue 31 (unusual tiredness or weakness); feeling faint 31; hallucinations 31, 42 (seeing, hearing, or feeling things that are not there); increased hand tremor 31; malaise 31 (general feeling of discomfort or illness); nausea or vomiting 15, 16, 31; numbness 31; sialorrhea 31 (excessive watering of mouth); weakness 31

Note: Nausea or vomiting occurs in nearly 80% of patients in early therapy 3 ; after several weeks, many patients develop tolerance to these effects 42.

Hallucinations are usually visual 42, 48 and, at early stages, non-threatening 42.

Incidence less frequent

Blepharospasm 15, 16, 31 (increased blinking or spasms of eyelids); blurred vision; cardiac irregularities 15, 16, 31 (fast, irregular, or pounding heart beat); diplopia 31 (double vision); hot flashes 31; mydriasis 31 (dilated pupils); neuropsychiatric effects, including paranoid ideation, psychotic episodes, and mental depression with or without suicidal tendencies 15, 16, 31, 48 (mood or mental changes); orthostatic hypotension 31, 48 (dizziness or lightheadedness when getting up from a lying or sitting position); palpitations 31 (fast or pounding heart beat); skin rash 31; trismus 31 (difficulty opening mouth); unusual weight gain or loss 31; urinary incontinence 31, 48 (loss of bladder control); urinary retention 15, 16, 31 (difficult urination)

Note: Orthostatic hypotension occurs in about 30% of patients at the initiation of levodopa therapy 20 ; tolerance may develop, and the severity of hypotension may decrease. 3

Cardiac arrhythmias3 , palpitations3 , and urinary retention3 may become less frequent when levodopa is administered concomitantly with a peripheral decarboxylase inhibitor, such as carbidopa.

Incidence rare

Agranulocytosis 31 (chills; fever; sore throat; unusual tiredness or weakness); duodenal ulcer 15, 16, 31 (stomach pain); edema 31 (swelling of face; swelling of feet or lower legs; unusual weight gain); gastrointestinal bleeding 31 (bloody or black, tarry stools; severe stomach pain; vomiting of blood or material that looks like coffee grounds); hemolytic anemia 15, 31 (back, leg, or stomach pain; fever; loss of appetite; pale skin; unusual tiredness or weakness); hypertension 15, 16, 31 (high blood pressure); oculogyric crisis 31 (inability to move eyes); phlebitis 31 (pain, tenderness, or swelling of foot or leg); priaprism 31 (prolonged, painful, inappropriate penile erection); seizures 31

Note: A causal relationship between levodopa therapy and seizures has not been established. 15, 31

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain 31; anorexia 15, 16, 31 (loss of appetite) 3, 15, 16, 31; dryness of mouth 15, 16, 31; flatulence (passing gas); nightmares 15, 16

Note: Nightmares may become less frequent when levodopa is combined with carbidopa because of the reduced dose requirements and unavailability of peripheral dopamine 13, 14.

Incidence less frequent

Constipation 15, 16, 48; diarrhea 15, 16, 31; flushing of skin 15, 16, 31; headache 15, 16, 31; hiccups 31; increased sweating 31, 48; insomnia 15, 16, 31 (trouble in sleeping); muscle twitching 15, 16, 31; unusual tiredness or weakness 15, 16, 31

Note: Constipation may become less frequent when levodopa is combined with a peripheral decarboxylase inhibitor. 14

Those not indicating need for medical attention

Incidence less frequent

Bitter taste 31; burning sensation of tongue 31; darkening in color of urine, saliva, or sweat 15, 16, 31

Overdose

For information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)-not necessarily inclusive:
Blepharospasm (increased blinking or spasms of eyelids)¾possible early sign of overdose 31

Treatment of overdose

Since there is no specific antidote for acute overdose with levodopa, treatment is symptomatic and supportive 15, 16 , with possible utilization of the following:
To decrease absorption¾Immediate gastric lavage. 15, 16

The value of dialysis in the treatment of overdose is not known. 15, 16

Monitoring¾Electrocardiographic monitoring for development of arrhythmias. 62

Specific treatment¾
Antiarrhythmic medication, if necessary. 15, 16

Pyridoxine in oral doses of 10 to 25 mg has been reported to reverse toxic and therapeutic effects of levodopa; however, in the treatment of acute overdosage, its usefulness has not been established. 15, 16

Supportive care¾
Judicious use of intravenous fluids. 62

Maintenance of airway. 62

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Levodopa (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to levodopa
Pregnancy¾No studies in humans; depressed growth in animal studies
Breast-feeding¾Distributed into breast milk; may inhibit lactation
Use in the elderly¾Reduced tolerance to effects of levodopa; caution in resuming normal activity, especially in patients with osteoporosis
Dental¾Possible difficulty in retention of full dentures
Other medications, especially cocaine, haloperidol, hydrocarbon inhalation anesthetics, MAO inhibitors, phenothiazines, pyridoxine and vitamin preparations containing pyridoxine, selegiline, and thioxanthenes; high-protein foods
Other medical problems, especially severe cardiovascular disease, glaucoma, melanoma (history of or suspected), mental depression, myocardial infarction with residual arrhythmias, peptic ulcer (history of), psychosis, severe pulmonary diseases, renal function impairment, or urinary retention
Proper use of this medication

>> Taking with meals or snacks for the first few months until tolerance to gastrointestinal effects develops; later, taking on an empty stomach for maximal absorption

>> Compliance with therapy; taking medication only as directed; not stopping medication unless ordered by physician

>> Maximum effectiveness of medication may not occur for several weeks or months after therapy is initiated

>> Proper dosing
Missed dose: Taking as soon as possible; skipping dose if next scheduled dose is within 2 hours; not doubling doses
>> Proper storage
Precautions while using this medication

Caution if any kind of surgery (including dental surgery) or emergency treatment is required

Patients with diabetes: May interfere with urine tests for sugar and ketones

>> Caution if drowsiness occurs

>> Caution when getting up suddenly from lying or sitting position; dizziness and fainting may occur

>> Avoiding foods or vitamin products containing pyridoxine (vitamin B 6); diminished levodopa effect when used with pyridoxine

>> Caution in resuming normal physical activities when condition has improved, especially for geriatric patients

Side/adverse effects

Signs of potential side effects, especially agitation; anxiety; ataxia; bruxism; choreiform and/or dystonic movements; confusion; delusions; dizziness; dysphagia; euphoria; fatigue; feeling faint; hallucinations; increased hand tremor; malaise; nausea or vomiting; numbness; sialorrhea; weakness; blepharospasm; blurred vision; cardiac irregularities; diplopia; hot flashes; mydriasis; neuropsychiatric effects, including paranoid ideation, psychotic episodes, and mental depression with or without suicidal tendencies; orthostatic hypotension; palpitations; skin rash; trismus; unusual weight gain or loss; urinary incontinence; urinary retention; agranulocytosis; duodenal ulcer; edema; gastrointestinal bleeding; hemolytic anemia; hypertension; oculogyric crisis; phlebitis; priaprism; seizures

Occasional darkening of urine, saliva, or sweat may be alarming to patient although medically insignificant

General Dosing Information

Levodopa therapy must be individualized and the dosage gradually titrated to the desired therapeutic level in order to reduce the high incidence of adverse reactions. 15, 16, 31

End-of-dose deterioration 45, 46 or "wearing off" periods 43 usually have a close temporal relationship to the timing of levodopa administration 39.

These effects may be alleviated for a time by shortening the dosing interval 41, 42 and reducing the size of individual doses 41.

However, compliance may be poor if the dosage regimen becomes too complex 42.

Although sometimes evident from the first dose, the benefit from initiation of levodopa therapy commonly increases over several weeks despite a fixed dosage regimen. In general, it takes 2 weeks for the final effects of a given change in levodopa treatment to "equilibrate" in the body so that the results of a dosage change can be assessed. 47

Postencephalitic and geriatric patients 11 often require and tolerate lower dosage levels than other parkinsonism patients 13.

The concurrent administration of a peripheral decarboxylase inhibitor such as carbidopa may permit the dose of levodopa to be reduced by up to 75% and yet achieve equal therapeutic results 32.

Carbidopa also reduces the adverse effect of pyridoxine on levodopa 32.

Similarly, concomitant administration of a COMT inhibitor such as tolcapone also may permit the dose of levodopa to be reduced. 59, 61

Other antiparkinsonian medications may be used concomitantly with or preceding levodopa therapy. Gradual dosage reduction of these medications is recommended during initiation of therapy with levodopa and after optimum dosage is reached to maintain proper control of the patient's condition. 16

When levodopa is to be discontinued, dosage should be tapered gradually to prevent the occurrence of a syndrome that resembles the neuroleptic malignant syndrome 9, 11 , with rhabdonecrosis, myoglobinuria, and renal failure 38.

Careful patient monitoring after withdrawal of levodopa will allow early diagnosis and treatment of neuroleptic malignant-like syndrome. 5, 13

Diet/Nutrition

Peripheral decarboxylation of levodopa to dopamine causes gastrointestinal side effects (such as nausea and vomiting) in up to 80% of patients in early therapy. 3 Levodopa may be given with meals or snacks for the first few months of therapy until tolerance to these side effects develops 3.

Later, levodopa should be given on an empty stomach for maximal absorption 3 ; administering levodopa on an empty stomach facilitates absorption and reduces competition with dietary proteins 48.

Also, standardizing the administration of levodopa with regard to meal times will optimize the rate of gastric emptying 44 ; some clinicians consider administering the levodopa dose 1 hour before or after eating food to be a practical approach 48.

High-protein diets should be avoided because protein degradation products compete with levodopa for transport across the intestinal epithelium and the blood-brain barrier, resulting in a decreased or erratic response to levodopa. Patients experiencing response fluctuations may be more susceptible to the interference that protein-containing meals have on the effectiveness of levodopa 46.

Strategies for reducing the competitive effects from dietary proteins include:
Assuring that the intake of normal amounts of protein be distributed equally throughout the day 13.

Introducing the redistribution diet, where protein intake is restricted to the evening meal only 48.

Imposing austere restrictions on total daily protein intake (£ 10 grams) for limited times in selected patients 46.

Adherence to a recommended dietary allowance of 0.8 gram of protein per kilogram of body weight per day, which seems to be a sufficient and safe restriction that does not affect the levodopa dose-response relationship 44.

In addition, pyridoxine (vitamin B 6) reverses the effects of levodopa 31, 46.

Vitamin products containing pyridoxine should be avoided; intake of foods containing large amounts of pyridoxine (such as bananas, egg yolks, lima beans, meats, peanuts, and whole grain cereals 49) may need to be limited.

For treatment of adverse effects

Immediate relief of nausea and vomiting may sometimes be obtained by reducing the daily dose, giving smaller individual doses at more frequent intervals, giving smaller doses concurrently with a

peripheral decarboxylase inhibitor such as carbidopa, or having patient take food shortly after each dose; 16 however, high-protein foods should be avoided since they may decrease levodopa's effect by competing for transport across the blood-brain barrier (see Absorption; Drug interactions and/or related problems).
Orthostatic hypotension may be alleviated by the use of nonpharmacologic measures such as elastic hosiery 3, 42 , and an increase in sodium 3, 42, 48 and fluid 42 intake. Some patients may require pharmacologic treatment with agents such as fludrocortisone 3, 48 or an alpha-adrenergic agonist. 42, 48 However, concomitant use of a peripheral decarboxylase inhibitor, such as carbidopa, reduces the incidence of this side effect 13.

Although drug holidays from levodopa therapy have been used to prevent some of the complications of long-term therapy and to enhance the efficacy of levodopa when therapy is reinstated 2 , such holidays are no longer considered justifiable 39, 41, 47 , as they may be associated with significant morbidity and life-threatening symptoms such as the neuroleptic malignant syndrome. 39

Oral Dosage Forms

LEVODOPA TABLETS USP

Usual adult and adolescent dose

Antidyskinetic¾
Oral, initially 250 mg two to four times a day; the daily dosage may be increased by an additional 100 to 750 mg at three- to seven-day intervals as tolerated, until the desired response is obtained. 15, 31

Note: Postencephalitic patients may be more sensitive to the effects of the usual adult dose. 13

Usual adult prescribing limits

8 grams daily. 15, 31

Usual pediatric dose

Children up to 12 years of age: Safety and efficacy have not been established. 15

Children 12 years of age and over: See Usual adult and adolescent dose.

Usual geriatric dose

See Usual adult and adolescent dose .

Note: Geriatric patients and patients with Alzheimer's disease may be more sensitive to the effects of the usual adult dose. 11

Strength(s) usually available

U.S.¾100 mg (Rx)[Larodopa]

250 mg (Rx)[Larodopa]

500 mg (Rx)[Larodopa]

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Preparation of dosage form:

A liquid formulation of levodopa may be prepared extemporaneously for use in dosage titration in patients who are extremely sensitive to small changes in the dose of levodopa 48.

(See Carbidopa and Levodopa monograph.)
Auxiliary labeling:

· May darken urine, saliva, or sweat.