APO-LEVOCARB
(Levodopa and Carbidopa) Tablets USP
100mg / 25mg, 250mg / 25mg
ANTIPARKINSON AGENT

Pharmacology:
Current evidence indicates that 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 apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the basal ganglia. This is thought to be the mechanism whereby levodopa relieves the symptoms of Parkinson's disease. When levodopa is administered orally it is rapidly converted to dopamine by decarboxylation in extra-cerebral tissues so that only a small portion of given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required to replace striatal dopamine deficiency. Most patients on levodopa therapy experience nausea and vomiting which requires very gradual introduction of the drug and limits frequently the therapeutic effect. Nausea and vomiting are probably related to the effect of dopa metabolites on the medullary emetic zone in the area postrema, which lies outside the blood-brain barrier for dopamine. The disabling cardiovascular adverse effects of levodopa are believed to be caused in part by the arrhythmogenic effect of levodopa and dopamine. 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 extracerebral tissues, administration of carbidopa with levodopa should prevent the extracerebral breakdown of levodopa, abolish or decrease those side-effects due to the peripheral actions of dopa metabolites, and increase the availability of levodopa to the brain. Clinical trials have confirmed that combined therapy with levodopa and carbidopa reduces the amount of levodopa required for optimum therapeutic benefit by about 75-80%, permits and 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. By increasing the availability of levodopa to the brain, dyskinesias and oscillations in performance ('on and off' phenomenon, akinesia paradoxica) tend to occur at lower dosages and sooner during combined therapy with fixed concentration levodopa and carbidopa combination products. Following simultaneous administration of levodopa and carbidopa in man, plasma levels and plasma half-life of levodopa were markedly increased over those found when the same dosage of levodopa was given alone, while plasma levels of dopamine and homovanillic acid were reduced or did not change. Nevertheless, the plasma levels vary greatly between patients. The evidence suggests that levodopa corrects the dopamine deficiency and the related akinesia of Parkinson's disease, probably by the formation of dopamine in the nigro-striatal dopaminergic nerves that remain functional. Although rigidity and to a considerable extent tremor and other symptoms also improve with levodopa therapy, it is thought that these symptoms may be related to a disturbed balance of neurotransmitters. Some of the known metabolites of levodopa are dopamine agonists but at least one metabolite has been demonstrated in animal studies to be a potent dopamine antagonist. Pyridoxine hydrochloride (vitamin B6), in oral doses of 10mg to 25mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

Indications:
APO-LEVOCARB (levodopa and carbidopa) is indicated for the treatment of Parkinson's syndrome with the exception of drug-induced parkinsonism. The administration of **APO-LEVOCARB** permits control of the symptoms of parkinsonism with the advantage of combined therapy being in a marked reduction in the incidence of nausea and vomiting allows for a more rapid induction of therapy (optimum dosage can usually be achieved within 2-3 weeks) and permits some patients to obtain adequate symptomatic relief who would otherwise be unable to tolerate an optimum dose of levodopa. Combined therapy with levodopa and carbidopa, however, increases the incidence of abnormal involuntary movements earlier in therapy and leads to an earlier appearance of oscillations in performance ('on and off' phenomenon, akinesia paradoxica). Therefore, when combined therapy with **APO-LEVOCARB** is used, it is important to aim at a maintenance dosage level which is free dyskinesias. Levodopa dose not arrest the progression of Parkinson's disease, and its adverse effects tent to increase with continuing use. Levodopa and combined therapy are therefore indicated only when their use improves the quality of life of the patients with Parkinson's disease.

Adverse Effects:
The most common serious adverse reactions occurring with levodopa and carbidopa combinations are abnormal involuntary movements. These reactions are dose-dependent and can be diminished by dosage reduction. The other serious adverse reactions are oscillations in performance psychiatric and cardiovascular.
Involuntary Movements: Such as choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be taken as early signs of excessive dosage. The appearance of these reactions should prompt a reduction of the dose administered.
Oscillations in Performance: Diurnal variations (end-of-dose akinesia), independent oscillations in akinesia with stereotyped dyskinesias, sudden akinetic crises related to dyskinesias, akinesia paradoxica (hypotonic freezing) and 'on and off' phenomenon. The mechanism of the oscillations in performance is not well established. It has been suggested that akinesia paradoxica might be the result of toxicity of levodopa upon progressively damaged receptors.
Psychiatric: Such as paranoid ideation, psychotic episodes, depression with or without development of suicidal tendencies and dementia. In depressed patients, levodopa produces an improvement in mood in only a small

number of individuals but when given regularly to bipolar depressed patients, levodopa may produce hypomania. Convulsions have occurred rarely, however, a causal relationship with levodopa and carbidopa combination has not been established. Less frequent adverse reactions are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, anorexia, nausea, vomiting and dizziness. Other adverse reactions that may occur during treatment with **APO-LEVOCARB** (levodopa and carbidopa) according to various systems are: increased libido, with serious antisocial behaviour, euphoria, lethargy, sedation, stimulation, fatigue and malaise, confusion, insomnia, nightmares, hallucinations and delusions, agitation and anxiety.

Neurologic: Ataxia, faintness, impairment of gait, headache, increased hand tremor, akinetic, episodes, "akinesia paradoxica", increase in the frequency and duration of the oscillations in performance, torticollis, trismus, tightness of the mouth, lips or tongue, oculogyric crisis, weakness, numbness, bruxism, priapism.

Gastrointestinal: Constipation, diarrhea, epigastric and abdominal distress and pain, flatulence; eructation, hiccups, sialorrhea; difficulty in swallowing, bitter taste, dry mouth; duodenal ulcer; gastrointestinal bleeding; burning sensation of the tongue.

Cardiovascular: Arrhythmias, hypotension, nonspecific ECG changes, flushing, phlebitis.

Hematologic: Hemolytic anemia, leukopenia, agranulocytosis.

Dermatologic: Sweating, edema, hair loss, pallor, rash, bad odour, dark sweat.

Musculoskeletal: Low back pain, muscle spasm and twitching, musculoskeletal pain.

Respiratory: Feeling of pressure in the chest, cough, hoarseness, bizarre breathing pattern, postnasal drip.

Urogenital: Urinary frequency, retention, incontinence, hematuria, dark urine, nocturia, and interstitial nephritis.

Special Senses: Blurred vision, diplopia, mydriasis, activation of latent Horner's syndrome.

Other: Hot flashes, weight gain or loss.

The following abnormalities in laboratory tests have been reported with levodopa and carbidopa combination. Elevations of blood urea nitrogen, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase of protein bound iodine. Occasional reduction in WBC, hemoglobin and hematocrit. Elevations of uric acid when the colorimetric method was used but not when uricase was used. Positive Coombs tests have been reported both with levodopa and carbidopa combination and with levodopa alone, but hemolytic anemia is extremely rare. Dark sweat and urine also have been reported both with levodopa alone, but were not considered indications for discontinuing therapy.

Warnings:

When a patient already receiving levodopa is switched to **APO-LEVOCARB** (levodopa and carbidopa), levodopa must be discontinued for at least 12 hours or more before **APO-LEVOCARB** is started. **APO-LEVOCARB** should be substituted at a dosage that will provide approximately 20% of the previous levodopa dosage **(see DOSAGE AND ADMINISTRATION).** The levodopa and carbidopa combination is not recommended for the treatment of drug-induced extrapyramidal reactions. The levodopa induced involuntary movements and 'on and off' phenomenon may appear earlier with combination therapy. As with levodopa, **APO-LEVOCARB** may cause involuntary movements and mental disturbances. The reactions are thought to be due to increased brain dopamine following administration of levodopa. Because carbidopa permits more levodopa to reach the brain thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with the levodopa and carbidopa combination than with levodopa alone. All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, or other serious antisocial behaviour. Patients with past or current psychoses should be treated with caution. Care should be exercised in administering **APO-LEVOCARB** to patients with a history of myocardial infraction 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. A symptom complex resembling the neuroleptic malignant syndrome, including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of levodopa/carbidopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. As with levodopa there is a possibility or upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Usage in Children: The safety of levodopa and carbidopa combinations in patients under 18 years of age has not been established.

Pregnancy and Lactation: Although the effects of levodopa and carbidopa combination on human pregnancy and lactation are unknown, both levodopa and combinations of levodopa and carbidopa have caused visceral and skeletal malformations in rabbits. Therefore, use of **APO-LEVOCARB** 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. **APO-LEVOCARB** should not be given to nursing mothers.

Precautions:

General Precautions: Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal functions are recommended during extended therapy in all patients receiving **APO-LEVOCARB** (levodopa and carbidopa). Patients with a history of convulsions should be treated with caution.

The levodopa and carbidopa combination should be administered cautiously to patients with severe cardiovascular, endocrine, hematologic, hepatic pulmonary (including bronchial asthma), or renal disease; or to patients with narrow angle glaucoma.

Physical Activity: Patients who improve while on therapy with **APO-LEVOCARB** should increase physical activities gradually, with caution, consistent with other medical considerations such as the presence of osteoporosis or phlebothrombosis.

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 levodopa and carbidopa combinations. The intraocular pressure should be well controlled and the patients monitored carefully for changes in intraocular pressure during therapy.

Contraindications:
As with levodopa, **APO-LEVOCARB** (levodopa and carbidopa) should not be given when administration of a sympathomimetic amine is contraindicated. **APO-LEVOCARB** is contraindicated in patients with known hypersensitivity to this drug. It is also contraindicated in the management of intention tremor and Huntington's chorea. Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

Drug Interactions:
Use in Patients on Antihypertensive Therapy: Symptomatic postural hypotension has been reported occasionally. For this reason, patients receiving antihypertensive drugs, along with **APO-LEVOCARB,** should be observed carefully for changes in pulse rate or blood pressure. When levodopa and carbidopa combination therapy is started, adjustment of the antihypertensive drug may be required.
Monoamine oxidase inhibitors and **APO-LEVOCARB** should not be given concomitantly, and these inhibitors must be discontinued two weeks prior to initiating therapy with **APO-LEVOCARB.**
Use in Patients on Psychoactive Drugs: If concomitant administration of psychoactive drugs such as phenothiazines and butyrophenones is necessary, such drugs should be administered with great caution and patients carefully observed for unusual adverse reactions. Also, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with **APO-LEVOCARB** should be carefully observed for loss of anti-parkinsonian effect.
Use with Anesthetics: When general anesthesia is required, **APO-LEVOCARB** should be discontinued the night before and reinstituted as soon as the patient is able to take medication by mouth.
Other Drugs: There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and **APO-LEVOCARB.**
Since levodopa competes with certain amino acids, the absorption of levodopa may be impaired in some patients on a high-protein diet.

Dosage:
In order to reduce the incidence of adverse reactions and achieve maximal benefits, therapy with **APO-LEVOCARB** (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 combined therapy with **APO-LEVOCARB** has a narrower therapeutic range than with 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 in indication of overdosage, requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesias. If a patients being treated with levodopa is switched to combined therapy with **APO-LEVOCARB,** levodopa must be discontinued at least twelve hours or more before therapy with **APO-LEVOCARB** is initiated. **APO-LEVOCARB** tablets are available in levodopa: carbidopa 4:1 ratio (**APO-LEVOCARB** 100mg/25mg**)**. Tablets of the two ratios may be given separately or combined as needed to provide the optimal dosage. Studies show that peripheral dopa decarboxylase is adequately inhibited by carbidopa at doses between 75 to 100 mg a day. Patients receiving less than 70 mg per day of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages greater than 200 mg is limited. For patients who require only low doses of levodopa, i.e., less than 700 mg, the 4:1 ratio levodopa and carbidopa combination may be helpful.
Induction of Therapy in Patients Not Receiving Levodopa:
Dosage is best initiated with one tablet of **APO-LEVOCARB** 100mg/25mg three times a day. This 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 **APO-LEVOCARB** 100/10 or 250/25 may be used as needed to provide the optimal dosage (usually 750-1250 mg of levodopa a day). Usually no patient should receive more than 1500 mg of levodopa a day. Some patients, including those with post encephalitic parkinsonism, are more sensitive to levodopa and require especially careful dosage adjustment.
Induction of Therapy in Patients Receiving Levodopa:
Levodopa must be discontinued at least twelve hours or more before levodopa and carbidopa combination is started. A dosage of levodopa and carbidopa combination 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 stopped. For example, if a patient is receiving 4000 mg of levodopa per day, the dosage of levodopa and carbidopa combination should not provide more than 750mg of levodopa per day divided into four to six doses. **APO-LEVOCARB** 100 mg/25 mg tablets should be used to start medication for patients requiring lower dosages of levodopa.
Adjustment and Maintenance of Therapy: The variability in dose response of patients is considerable. Some individuals may experience oscillations in response with a diurnal rhythm of periods of symptomatic control alternating with periods of akinesia (end-of-dose) with essentially a return of Parkinson's symptoms. These can frequently be corrected by rescheduling of individual doses. A low protein diet tends to potentiate and stabilize

the effects of levodopa, whereas a high protein diet may decrease the effect of levodopa, although with combined therapy this effect may be less prominent. However, the predominant limiting factor in the success of treatment with levodopa and carbidopa combination is the occurrence of involuntary movements. These frequently can be controlled by reducing the dosage of levodopa and varying the frequency of individual doses. A progressive decrease in the threshold for dyskinetic manifestations and an increase in the incidence of oscillations in performance have been reported after a certain time on levodopa therapy. Different types of oscillations in performance have been described, including sudden akinetic crises marked by a rapid change-over ('on and off' phenomenon) related to patterns of involuntary movements and hypotonic akinesia (akinesia paradoxica). Dyskinetic manifestations and oscillations in performance appear earlier in the course of combined treatment with levodopa and carbidopa combination than with levodopa alone. In an attempt to try to avoid the emergence, or decrease the incidence of these manifestations, it has been recommended that, after the initial induction period, the dosage of levodopa should be reduced very slowly at the rate of about 50 mg every month, over period of few months, to a maintenance level without dyskinesias. **APO-LEVOCARB** 100 mg/25 mg or 100mg/10 mg tablets may be useful for patients who required small adjustments in dosage. Patients should be monitored closely particularly during the dose adjustment period. The incidence of blepharospasm (spasmodic winking or contraction of the orbicularis oculi muscle) may be an early sign of excess dosage in some patients. Current evidence indicates that other standard antiparkinsonian drugs may be continued while the levodopa and carbidopa combination is being administered although their dosage may have to be adjusted. If general anesthesia is required, therapy with levodopa and carbidopa combination may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual a daily dosage may be administered as soon as the patient is able to take oral medication.

Symptoms and Treatment of Overdosage:
Management of acute overdosage with **APO-LEVOCARB** (levodopa and carbidopa) is basically the same as management of acute overdosage with levodopa alone. Pyridoxine is not effective in reversing the actions of levodopa and carbidopa combination. 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 **APO-LEVOCARB** should be taken into consideration. To date, no experience has been reported with dialysis, hence, its value in over dosage is not known.

Availability of Dosage Forms:
APO-LEVOCARB 100mg/25 mg: Each yellow, oval biconvex tablet, one side scored and engraved "100 25" and the other side engraved "APO", contains 100mg of levodopa and 25 mg of carbidopa expressed as anhydrous carbidopa. Available in HDPE bottles of 100s.
APO-LEVOCARB 250mg/ 25 mg : Each blue, oval, biconvex tablets, with one side scored and engraved '250 25" and the other side engraved "APO", contains 250mg of levodopa and 25mg of carbidopa expressed s anhydrous carbidopa. Available in HDPE bottles of 100s.

Storage Conditions:
Store below 25°C

Manufacturer:
Apotex Inc, 150 Signet Drive, Weston (Toronto), Ontario, Canada, M9L 1T9.

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