PARIDOPA®

(Levodopa/Carbidopa/Entacapone)

پیری ڈوپا

COMPOSITION

Paridopa 50/12.5/200 Tablet

Each film coated tablet contains:

Levodopa.....50mg
Carbidopa.....12.5mg
Entacapone.....200mg

Paridopa 100/25/200 Tablet

Each film coated tablet contains:

Levodopa.....100mg
Carbidopa.....25mg
Entacapone.....200mg

Paridopa 200/50/200 Tablet

Each film coated tablet contains:

Levodopa.....200mg
Carbidopa.....50mg
Entacapone.....200mg

(As per innovator's specs.)

DESCRIPTION

Paridopa is a combination of carbidopa, levodopa, and entacapone for the treatment of Parkinson's disease. Levodopa is an aromatic amino acid, which is a metabolic pre-cursor of dopamine and is designated chemically as (-)-L-α-amino-β-(3, 4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$. Carbidopa is an inhibitor of aromatic amino acid decarboxylation and designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3, 4¬ dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$. Entacapone is a catechol-O-methyl transferase (COMT) inhibitor. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$.

CLINICAL PHARMACOLOGY

Mechanism of Action

Levodopa

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 because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and is presumably converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves the symptoms of Parkinson's disease.

Carbidopa

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for delivery to the brain and limits adverse effects due to high peripheral dopamine levels such as nausea, vomiting and cardiovascular effects.

Entacapone

When decarboxylation of levodopa is prevented by carbidopa, cathechol-O-methyl transferase (COMT) becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD), a potentially harmful metabolite. Entacapone is a reversible, specific and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa. Entacapone slows the clearance of levodopa from the bloodstream resulting in an increased area under the curve (AUC) in the pharmacokinetic profile of levodopa. Consequently, the clinical response to each dose of levodopa is enhanced and prolonged reducing the potential for end-of-dose response fluctuations observed with Levodopa. Response fluctuations are characterized by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period.

Pharmacodynamics:

The evidence of the therapeutic effects of Levodopa/Carbidopa/Entacapone is based on two phase III double -blind studies, in which 376 Parkinson's disease patients with end-of-dose motor fluctuations received either entacapone or placebo with each levodopa/DDC inhibitor dose. Daily ON time with and without entacapone was recorded in home-diaries by patients. In the first study, entacapone increased the mean daily ON time by 1h 20 min (CI 95% 45 min, 1h 56 min) from baseline. This corresponded to an 8.3% increase in the proportion of daily ON time. Correspondingly, the decrease in daily OFF time was 24% in the entacapone group and 0% in the placebo group. In the second study, the mean proportion of daily ON time increased by 4.5% (CI 95% 0.93%, 7.97%) from baseline. This is translated to a mean increase of 35 min in the daily ON time. Correspondingly, the daily OFF time decreased by 18% on entacapone and by 5% on placebo. Because the effects of Levodopa/Carbidopa/Entacapone tablets are equivalent with entacapone 200 mg tablet administered concomitantly with the commercially available standard release carbidopa/levodopa preparations in corresponding doses these results are applicable to describe the effects of Levodopa/Carbidopa/Entacapone as well.

Pharmacokinetics

Absorption and Distribution:

Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its Cmax. The food-effect on the combination tablet has not been evaluated. Because levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients after eating a high protein meal. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa.

Levodopa

Levodopa is bound to plasma protein only to a minor extent (about 10% to 30%). The distribution volume of levodopa is 0.36-1.6 L/kg.

Carbidopa

Following administration of combination tablet as a single dose to healthy male and female subjects, the peak concentration of carbidopa is reached within 2.5 hours to 3.4 hours on average. The mean Cmax ranges from about 40 nanogram per mL to 225 nanogram per mL and the mean AUC from 170 nanogram•h per mL to 1,200 nanogram•h per mL, with different formulation strengths providing 12.5 mg, 25 mg, 37.5 mg, or 50 mg of carbidopa. Carbidopa is approximately 36% bound to plasma proteins. No data of volume of distribution of carbidopa are available.

Entacapone

Following administration of combination tablet as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 0.8 hour to 1.2 hours on average. The mean Cmax of entacapone was about 1,200 nanogram per mL to 1,500 nanogram per mL and the AUC 1,250 nanogram•h per mL to 1,750 nanagram•h per mL after administration of different formulation strengths all providing 200 mg of entacapone. The plasma protein binding of entacapone is 98% over the concentration range of 0.4 mcg per mL to 50 mcg per mL. Entacapone binds mainly to serum albumin. The distribution volume of entacapone 0.27 L/kg.

Metabolism:

Levodopa

Levodopa is extensively metabolized to various metabolites. Two major pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by COMT.

Carbidopa

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4 hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates.

Entacapone

Entacapone is almost completely metabolized prior to excretion with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the cis-isomer, the only active metabolite.

The glucuronides account for 95% of all urinary metabolites (70% as parent and 25% as cis-isomer glucuronides). The glucuronide conjugate of the cis-isomer is inactive. Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

Elimination:

Levodopa

The elimination half-life of levodopa, the active moiety of antiparkinsonian activity, was 1.7 hours (range 1.1 hours to 3.2 hours).

Carbidopa

The elimination half-life of carbidopa was on average 1.6 hours to 2 hours (range 0.7 hour to 4.0 hours). Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone

The elimination half-life of entacapone was on average 0.8 hour to 1 hour (0.3 hour to 4.5 hours). Entacapone and the cis-isomer are eliminated in the urine as glucuronide conjugates.

INDICATIONS

Paridopa is indicated for the treatment of Parkinson's disease.

Paridopa can be used:

• To substitute (with equivalent strengths of each of the three components) carbidopa/levodopa and entacapone previously administered as separate products.

• To replace carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" response fluctuations and when they have been taking a total daily dose of levodopa of 600 mg or less and have not been experiencing dyskinesias.

DOSAGE AND ADMINISTRATION

The optimum daily dosage of Paridopa must be determined by careful titration in each patient. The maximum recommended daily dose of Paridopa depends on the strength used. The maximum number of tablets to be used in a 24-hour period is less with the highest strength (Paridopa 200/50/200) than with lower strengths (see Table 1). Patients should be instructed to take only one Paridopa tablet per dose administration.

When more levodopa is required, an increase in the frequency of doses and/or the use of an alternative strength of Paridopa should be considered, within the dose recommendations.

When less levodopa is required, the total daily dose of Paridopa should be reduced either by decreasing the frequency of administration by extending the time between doses, or by decreasing the strength of Paridopa at an administration.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 mg per day to 100 mg per day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Table 1: Maximum Recommended Dose of Paridopa in a 24-hour Period

Paridopa Dosage Strength*	Maximum Number of Tablets in a 24-hour Period
Levodopa 50mg+ Carbidopa 12.5mg + Entacapone 200mg Tablet Levodopa 100mg + Carbidopa 25mg + Entacapone 200 mg Tablet	8
Levodopa 200 mg+ Carbidopa 50mg + Entacapone 200mg Tablet	6

NB: *Strengths are represented with the corresponding amounts of Levodopa present

Paridopa should be used as a substitute for patients already stabilized on equivalent doses of carbidopa/levodopa and entacapone. However, some patients who have been stabilized on a given dose of carbidopa/levodopa may be treated with Paridopa, if a decision has been made to add entacapone. Therapy should be individualized and adjusted according to the desired therapeutic response.

Converting Patients from Carbidopa, Levodopa, and Entacapone to Paridopa

Patients currently treated with entacapone 200 mg with each dose of non-extended release carbidopa/levodopa tablet, can switch to the corresponding strength of Paridopa containing the same amounts of levodopa and carbidopa. For example, patients receiving one tablet of carbidopa/levodopa 25 mg/100 mg and one tablet of entacapone 200 mg at each administration can switch to a single Paridopa 100 tablet (containing 25 mg of carbidopa, 100 mg of levodopa and 200mg of entacapone).

Converting Patients from Carbidopa and Levodopa Products to Paridopa

There is no experience in transferring patients currently treated with extended release formulations of carbidopa/levodopa, or carbidopa/levodopa products that are not combined in a 1:4 ratio of carbidopa to levodopa. Patients with a history of moderate or severe dyskinesias or taking more than 600 mg of the levodopa component per day are likely to require a reduction in their daily levodopa dose when entacapone is added.

Because dose adjustment of the individual carbidopa or levodopa component is not possible with fixed-dose products, initially titrate patients to a dose that is tolerated and that meets their individual therapeutic need using a separate carbidopa/levodopa tablet (1:4 ratios) plus an entacapone tablet. Once the patient's individual dose of carbidopa/levodopa plus entacapone dose has been established using two separate tablets; switch the patient to a corresponding single tablet of Paridopa. When less levodopa is required, reduce the total daily dosage of carbidopa/levodopa either by decreasing the strength of Paridopa at each administration or by decreasing the frequency of administration by extending the time between doses.

Concomitant Use with Other Anti-Parkinson's Disease Drugs

Anticholinergic agents, dopamine agonists, monoamine oxidase (MAO) - B inhibitors, amantadine, and other standard drugs for Parkinson's disease may be used concomitantly while Paridopa is being administered; however, dosage adjustments of the concomitant medication or Paridopa may be required.

Decrease or Interruption of Dosing

Avoid interruption of Paridopa dosing because hyperpyrexia has been reported in patients who suddenly discontinue or reduce their use of levodopa.

Discontinuation of Paridopa therapy

If Paridopa treatment (levodopa/carbidopa/entacapone) is discontinued and the patient is transferred to levodopa/DDC inhibitor therapy without entacapone, it is necessary to adjust the dosing of other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms.

Dosing considerations in Special populations

Renal Impairment

Paridopa therapy should be administered cautiously to patients in severe renal impairment including those receiving dialysis and a longer dosing interval of Paridopa may be considered for patients on dialysis.

Hepatic Impairment or Biliary Obstruction

Paridopa should be administered cautiously to patients with biliary obstruction or mild to moderate hepatic impairment (Child Pugh Class A and B) since biliary excretion appears to be the major route of excretion of entacapone and hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200 mg entacapone was administered alone. The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both in the absorption and elimination phases. Paridopa must not be used in patients with severe hepatic impairment. (Child Pugh Class C)

Important Administration Instructions

Do not split, crush or chew Paridopa tablets. Administer only one tablet at each dosing interval. All strengths of Paridopa contain 200 mg of entacapone. Combining multiple tablets or portions of tablets to achieve a higher levodopa dose may lead to an overdose of entacapone.

Administer Paridopa with or without food. However, a high protein meal may delay the absorption of levodopa.

CONTRAINDICATIONS

Paridopa is contraindicated in patients:

• Taking nonselective monoamine oxidase (MAO) inhibitors (e.g., phenelzine and tranylcypromine). These nonselective MAO inhibitors must be discontinued at least two weeks prior to initiating therapy with Paridopa.
• With narrow-angle glaucoma.
• With severe hepatic impairment
• With pheochromocytoma
• With hypersensitivity to the active substances levodopa, carbidopa or entacapone

WARNINGS AND PRECAUTIONS

Falling Asleep During Activities of Daily Living and Somnolence

Patients with Parkinson's disease treated with levodopa/carbidopa/entacapone combination or other carbidopa/levodopa products have reported suddenly falling asleep without prior warning of sleepiness while engaged in activities of daily living (including the operation of motor vehicles). Some of these events have been reported to occur up to one year after initiation of treatment. Before initiating treatment with Paridopa, advise patients of the potential to develop drowsiness and consider factors that may increase this risk such as use of concomitant sedating medications and the presence of sleep disorders. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Paridopa should ordinarily be discontinued. If the decision is made to continue Paridopa, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hypotension, Orthostatic Hypotension and Syncope

Hypotension, orthostatic hypotension, and syncope are observed in patients treated with drugs that increase central dopaminergic tone including Paridopa. Paridopa should be used with caution in patients taking other drugs that may cause orthostatic hypotension.

Dyskinesia

Dyskinesia (involuntary movements) may occur or be exacerbated at lower dosages and sooner with Paridopa than with preparations containing only carbidopa and levodopa. The occurrence of dyskinesias may require dosage reduction. Although decreasing the dose of levodopa may ameliorate this side effect, many patients may continue to experience frequent dyskinesia despite a reduction in their dose of levodopa.

Depression and Suicidality

All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

Hallucinations and/or Psychotic-Like Behavior

Dopaminergic therapy in patients with Parkinson's disease has been associated with hallucinations. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials. Hallucinations have also led to hospitalization in some cases. Agitation has also been reported.

Impulse Control and/or Compulsive Behaviors

Patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications generally used for the treatment of Parkinson's disease

and which increase central dopaminergic tone, including entacapone taken with levodopa and carbidopa. In some cases, these urges were reversible when the dose of anti-Parkinson medications was reduced or discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with entacapone. Physicians should consider dose reduction or stopping Paridopa if a patient develops such urges while taking Paridopa.

Withdrawal emergent hyperpyrexia and confusion

Cases of hyperpyrexia and confusion resembling neuroleptic malignant syndrome (NMS) have been reported in association with dose reduction or withdrawal of therapy with carbidopa, levodopa and entacapone. Hyperpyrexia and confusion are uncommon but they may be life-threatening with a variety of features, including hyperpyrexia/fever/hyperthermia, muscle rigidity, involuntary movements, altered consciousness/-mental status changes, delirium, autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension, and abnormal laboratory findings (e.g., creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin). If a patient needs to discontinue or reduce their daily dose of Paridopa, the dose should be decreased slowly.

Diarrhea and Colitis

In clinical trials diarrhea has been reported with entacapone in combination with levodopa and dopa decarboxylase inhibitors. In patients treated with entacapone, diarrhea was generally mild to moderate in severity but was regarded as severe in a few cases. Diarrhea generally resolved after discontinuation of entacapone. Typically, diarrhea presents within 4 to 12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment. Diarrhea may be associated with weight loss, dehydration, and hypokalemia. Postmarketing experience has shown that diarrhea may be a sign of drug-induced microscopic colitis, primarily lymphocytic colitis. In these cases diarrhea has usually been moderate to severe, watery and non-bloody, at times associated with dehydration, abdominal pain, weight loss, and hypokalemia. In the majority of cases, diarrhea and other colitis-related symptoms resolved or significantly improved when entacapone treatment was stopped. In some patients with biopsy confirmed colitis, diarrhea had resolved or significantly improved after discontinuation of entacapone but recurred after retreatment with entacapone. If prolonged diarrhea is suspected to be related to Paridopa, the drug should be discontinued and appropriate medical therapy considered.

Rhabdomyolysis

Cases of severe rhabdomyolysis have been reported with entacapone when used in combination with carbidopa and levodopa. Severe prolonged motor activity including dyskinesia may possibly account for rhabdomyolysis. Most of the cases were manifested by myalgia and increased values of creatine phosphoki-nase (CPK) and myoglobin. Some of the reactions also included fever and/or alteration of consciousness. It is also possible that rhabdomyolysis may be a result of the syndrome described in Withdrawal-Emergent Hyperpyrexia and Confusion.

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 providers are advised to monitor for melanomas frequently and on a regular basis when using Paridopa, for any indication. Ideally, periodic skin examination should be performed by appropriately qualified individuals (e.g., dermatologists).

Interaction with Drugs Metabolized by COMT

Drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rate, arrhythmia, and/or increased blood pressure.

Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve upon drug discontinuation, but complete resolution does not always occur. Although these adverse reactions may be related to the ergoline structure of these compounds, a possible causal role of non-ergot derived drugs (e.g., entacapone, levodopa), which increase dopaminergic activity, has also been considered.

Peptic Ulcer Disease

As with levodopa, treatment with Paridopa may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer. Caution is advised.

Hepatic Impairment

Patients with hepatic impairment should be treated with caution. As with levodopa, periodic evaluation of hepatic function is recommended during extended therapy. See DOSAGE AND ADMINISTRATION and USE IN SPECIAL POPULATIONS.

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Paridopa than with levodopa. Paridopa may cause a false-positive reaction for urinary ketone bodies when a test tape 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 on carbidopa/levodopa 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 carbidopa/levodopa therapy.

Progressive weight loss

For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered.

Patients with open-angle (wide-angle glaucoma)

Patients with chronic wide-angle glaucoma may be treated with Paridopa with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure. Paridopa is contraindicated in patients with angle-closure (narrow-angle) glaucoma.

Effects on ability to drive and use machines

Paridopa may have a major influence on the ability to drive and use machines. Levodopa, carbidopa and entacapone together may cause dizziness and symptomatic orthostatism. Therefore, caution should be exercised when driving or using machines. Patients being treated with Paridopa and presenting with somnolence and/or sudden sleep onset episodes must be instructed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes have resolved.

General precautions

Paridopa therapy should be administered cautiously to patients with ischemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal or endocrine disease or history of convulsions. In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias; cardiac function should be monitored with particular care during the period of initial dose adjustments. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Paridopa.

ADVERSE REACTIONS

Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Thrombocytopenia
Metabolism and nutrition disorders	
Common:	Weight decreased, decreased appetite
Psychiatric disorders	
Common:	Depression, hallucination, confusional state, abnormal dreams, anxiety, insomnia
Uncommon:	Psychosis, agitation
Not known:	Suicidal behaviour
Nervous system disorders	
Very common:	Dyskinesia
Common:	Parkinsonism aggravated (e.g. bradykinesia), tremor, on and off phenomenon, dystonia, mental impairment (e.g. memory impairment, dementia), somnolence, dizziness, headache
Not known:	Neuroleptic malignant syndrome
Eye disorders	
Common:	Blurred vision
Cardiac disorders	
Common:	Ischemic heart disease events other than myocardial infarction (e.g. angina pectoris), irregular heart rhythm
Uncommon:	Myocardial infarction
Vascular disorders:	
Common:	Orthostatic hypotension, hypertension
Uncommon:	Gastrointestinal haemorrhage
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea
Gastrointestinal disorders	
Very common:	Diarrhoea, nausea
Common:	Constipation, vomiting, dyspepsia, abdominal pain and discomfort*, dry mouth
Uncommon:	Colitis, dysphagia
Hepatobiliary disorders	
Uncommon:	Hepatic function test abnormal
Not known:	Hepatitis with mainly cholestatic features
Skin and subcutaneous tissue disorders	
Common:	Rash, hyperhidrosis
Uncommon:	Discolourations other than urine (e.g. skin, nail, hair, sweat)
Rare:	Angioedema
Not known:	Urticaria
Musculoskeletal and connective tissue disorders	
Very common:	Muscle, musculoskeletal and connective tissue pain
Common:	Muscle spasms, arthralgia
Not known:	Rhabdomyolysis
Renal and urinary disorders	
Very common:	Chromaturia
Common:	Urinary tract infection

DRUG INTERACTIONS

MAO Inhibitors

Patients receiving nonselective MAO inhibitors and carbidopa, levodopa and entacapone may be at risk of increased adrenergic tone. Therefore, the use of Paridopa is contraindicated in patients receiving nonselective MAO inhibitors. Selective MAO-A or MAO-B inhibitors may be used concomitantly with caution.

Drugs Metabolized by Catechol-O-Methyltransferase (COMT)

Drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Antihypertensive Agents

Symptomatic postural hypotension has occurred when carbidopa/levodopa was added to the treatment of patients receiving antihypertensive drugs. When starting therapy with Paridopa, dosage adjustment of antihypertensive drug may be required.

Tricyclic Antidepressants

There have been reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa/levodopa. Caution is advised.

Dopamine D2 Receptor Antagonists

Dopamine D2 receptor antagonists (e.g., metoclopramide, and antipsychotics phenothiazines, butyrophe-nones, risperidone) may reduce the therapeutic effects of levodopa.

Isoniazid

Isoniazid may reduce the therapeutic effects of levodopa, a dose increase may be necessary.

Phenytoin

The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin. Patients taking phenytoin with carbidopa/levodopa should be carefully observed for loss of therapeutic response. Paridopa dosage should be increased as clinically needed in patients receiving phenytoin.

Papaverine

The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by papaverine. Patients taking papaverine with carbidopa/levodopa should be carefully observed for loss of therapeutic response. Paridopa dosage should be increased as clinically needed in patients receiving papaverine.

Iron Salts

Iron salts or multi vitamins containing iron salts should be coadministered with caution. Iron salts can form chelates with levodopa, carbidopa and entacapone and consequently reduce bioavailability of levodopa, carbidopa and entacapone. Therefore, Paridopa and iron preparations should be taken at least 2-3 hours apart

Drugs Known to Interfere with Biliary Excretion, Glucuronidation, and Intestinal Beta-glucuronidase

As most entacapone excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase are given concurrently with entacapone. These include probenecid, cholestyramine, and some antibiotics (e.g., erythromycin, rifampicin, ampicillin and chloramphenicol).

Drugs Metabolized via CYP2C9 (e.g. warfarin)

The dosage of Paridopa should be adjusted as clinically needed in patients using other drugs metabolized via CYP2C9. In an interaction study in healthy volunteers, entacapone increased the AUC of R-warfarin on average by 18%, and the INR values on average by 13%. Cases of increased INR in patients concomitantly using warfarin have been reported during the post-approval use of entacapone. Thus, monitoring of INR is recommended when Paridopa treatment is initiated for patients receiving warfarin.

USE IN SPECIAL POPULATIONS

Pregnancy

US FDA Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. In animals, administration of carbidopa-levodopa or entacapone during pregnancy was associated with developmental toxicity, including increased incidences of fetal malformations. Paridopa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Carbidopa and entacapone are excreted in rat milk. It is not known whether entacapone, carbidopa, or levodopa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Paridopa is administered to a nursing woman.

Pediatric population

The safety and efficacy of Paridopa in children aged below 18 years have not been established. No data are available.

Elderly

There are no overall differences in safety or effectiveness between elderly and younger patients; however, greater sensitivity of some older individuals cannot be excluded. No dose adjustment of Paridopa is required for older people.

Patients with renal impairment

Renal impairment does not affect pharmacokinetics of entacapone. There are no studies on the pharmacokinet-ics of levodopa and carbidopa in patients with renal impairment. Paridopa therapy should be administered cautiously to patients in severe renal impairment including those receiving dialysis therapies (See DOSAGE & ADMINISTRATION)

Patients with hepatic impairment

There are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment. Paridopa should be administered cautiously to patients with biliary obstruction or mild to moderate hepatic impairment (Child Pugh Class A and B); since biliary excretion appears to be the major route of excretion of entacapone and hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200 mg entacapone was administered alone. The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) leading to an increased plasma concentration of entacapone both in the absorption and elimination phases. Paridopa must not be used in patients with severe hepatic impairment (Child Pugh Class C).

OVERDOSE

There are very few cases of overdose with levodopa reported in the published literature. Based on the available information, the acute symptoms of levodopa and dopa decarboxylase inhibitor overdose can be expected to arise from dopaminergic overstimulation. Doses of a few grams may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g., hypotension, tachycardia) and more severe psychiatric problems at higher doses. An isolated report of rhabdomyolysis and another of transient renal insufficiency suggest that levodopa overdose may give rise to systemic complications, secondary to dopaminergic overstimulation. COMT inhibition by entacapone treatment is dose-dependent. A massive overdose of entacapone may theoretically produce a 100% inhibition of the COMT enzyme in people, thereby preventing the O-methylation of endogenous and exogenous catechols.

Management of Overdosage

Hospitalization is advised, and general supportive measures should be employed, along with immediate gastric lavage and repeated doses of charcoal over time. This may hasten the elimination of entacapone in particular, by decreasing its absorption and reabsorption from the GI tract. Intravenous fluids should be administered judiciously and an adequate airway maintained. Respiratory, circulatory and renal function should be monitored and appropriate supportive measures employed. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs, increasing the risk of drug interactions (especially catechol-structured drugs) should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known. Hemodialysis or hemoperfusion is unlikely to reduce entacapone levels due to its high binding to plasma proteins. Pyridoxine is not effective in reversing the actions of Paridopa.

PRESENTATION

Paridopa 50/12.5/200mg : Pack of 30 tablets.
Paridopa 100/25/200mg : Pack of 10 & 30 tablets.
Paridopa 200/50/200mg : Pack of 30 tablets.

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

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