SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Carbidopa and Levodopa Tablets

PARDOPA

2. Quality and Quantitative Composition

Each uncoated tablet contains:

Carbidopa BP equivalent to Anhydrous Carbidopa 25mg

Levodopa BP.....250 mg

For excipients see 6.1.

3. Pharmaceutical Form

Tablet

White to off white, flat, circular, bevel edged. Uncoated tablets with break line on one surface.

4. Clinical Particulars

4.1 Therapeutic indications:

Antiparkinsonian agent

For treatment of Parkinson's disease and syndrome

4.2 Posology and method of administration:

To be taken orally.

The optimum daily dosage must be determined by careful titration in each patient.

These Tablets are available in a ratio of 1:4 or 1:10 of carbidopa to levodopa to provide facility for fine dosage titration for each patient.

General Considerations

Studies show that the peripheral dopa-decarboxylase is fully inhibited (saturated) by carbidopa at doses between 70 and 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Standard antiparkinsonian drugs, other than levodopa alone, may be continued while Carbidopa and Levodopa ' is being administered, although their dosage may have to be adjusted.

Because both therapeutic and adverse effects are seen more rapidly with Carbidopa and Levodopa ' than with levodopa, patients should be carefully monitored during the dosage adjustment period. Involuntary movements, particularly blepharospasm, are a useful early sign of excess dosage in some patients.

Patients not receiving levodopa

Dosage may be best initiated with one tablet 25 mg/100 mg' three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet of Carbidopa and Levodopa 12.5 mg/50 mg' or every day or every other day, as necessary, until a dosage equivalent of eight tablets of 25 mg/100 mg' a day is reached.

If Carbidopa and Levodopa 10 mg/100 mg Tablets' or Carbidopa and Levodopa 12.5 mg/50 mg tpablets are used, dosage may be initiated with one tablet three or four times a day. Titration upward may be required in some patients to achieve optimum dosage of carbidopa. The dosage may be increased by one tablet every day or every other day until a total of eight tablets (two tablets q.d.s.) is reached.

Response has been observed in one day, and sometimes after one dose. Fully effective doses usually are reached within seven days as compared to weeks or months with levodopa alone.

Carbidopa and Levodopa 12.5 mg/50 mg Tablets' or Carbidopa and Levodopa 10 mg/100 mg Tablets' may be used to facilitate dosage titration according to the needs of the individual patient.

Patients receiving levodopa

Discontinue levodopa at least 12 hours (24 hours for slow-release preparations) before starting therapy with Carbidopa and Levodopa '. The easiest way to do this is to give Carbidopa and Levodopa ' as the first morning dose after a night without any levodopa. The dose of Carbidopa and Levodopa ' should be approximately 20% of the previous daily dosage of levodopa.

Patients taking less than 1,500 mg levodopa a day should be started on one tablet of Carbidopa and Levodopa Plus 25 mg/100 mg' three or four times a day dependent on patient need. The suggested starting dose for most patients taking more than 1,500 mg levodopa a day is one tablet of Carbidopa and Levodopa 25 mg/250 mg' three or four times a day.

Maintenance

Therapy with Carbidopa and Levodopa ' should be individualized and adjusted gradually according to response.

When a greater proportion of carbidopa is required, each tablet of Carbidopa and Levodopa 10 mg/100 mg may be replaced with a tablet of 25 mg/100 mg' or Carbidopa and Levodopa 12.5 mg/50 mg.

When more levodopa is required, Carbidopa and Levodopa 25 mg/250 mg tablets should be substituted at a dosage of one tablet three or four times a day. If necessary, the dosage of Carbidopa and Levodopa 25 mg/250 mg tablets may be increased by one tablet every day or every other day to a maximum of eight tablets a day. Experience with a total daily dosage greater than 200 mg carbidopa is limited.

Patients receiving levodopa with another decarboxylase inhibitor

When transferring a patient to Carbidopa and Levodopa ' from levodopa combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before Carbidopa and Levodopa ' is started. Begin with a dosage of Carbidopa and Levodopa ' that will provide the same amount of levodopa as contained in the other levodopa/decarboxylase inhibitor combination.

Patients receiving other antiparkinsonian agents

Current evidence indicates that other antiparkinsonian agents may be continued when Carbidopa and Levodopa ' is introduced, although dosage may have to be adjusted in line with manufacturers' recommendations.

Use in children

The safety of Carbidopa and Levodopa ' in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

Use in the elderly

There is wide experience in the use of this product in elderly patients. The recommendations set out above reflect the clinical data derived from this experience.

4.3 Contraindications:

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa and Levodopa '. These inhibitors must be discontinued at least two weeks before starting Carbidopa and Levodopa '. It may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. Selegiline hydrochloride).

It is contraindicated in patients with narrow-angle glaucoma and in patients with known hypersensitivity to any component of this medication.

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

Use in patients with severe psychoses.

4.4 Special warning and precautions:

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

It should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastro-intestinal hemorrhage).

Care should be exercised when it is administered to patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial Behaviour. Patients with current psychoses should be treated with caution.

Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

As with levodopa, it may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone should be observed carefully when it is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Carbidopa and Levodopa ' may cause a recurrence. A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Therefore, any abrupt dosage reduction or withdrawal of Carbidopa and Levodopa ' should be carefully observed, particularly in patients who are also receiving neuroleptics.

Concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect. Patients with a history of convulsions should be treated with caution.

As with levodopa, periodic evaluation of hepatic, haematopoetic, cardiovascular and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with Carbidopa/Levodopa Orion, provided the intra-ocular pressure is well controlled and the patient monitored carefully for changes in intra-ocular pressure during therapy.

If general anaesthesia is required, therapy with Carbidopa/Levodopa Orion may be continued for as long as the patient is permitted to take fluids and medication by mouth. If therapy has to be stopped temporarily, Carbidopa/Levodopa Orion may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 fold higher). It is unclear whether the increased risk observed was due to Parkinson's disease, or other factors such as drugs used to treat Parkinson's disease. Therefore patients and providers are advised to monitor for melanomas on a regular basis when using Carbidopa/Levodopa Orion for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Laboratory Tests

Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Carbidopa/Levodopa Orion than with levodopa. Transient abnormalities include elevated levels of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase.

Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported.

Positive Coombs' tests have been reported, both with Carbidopa/Levodopa Orion and levodopa alone.

Carbidopa/Levodopa Orion may cause a false positive result when a dipstick is used to test for urinary ketone; and this reaction is not altered by boiling the urine. The use of glucose oxidase methods may give false negative results for glycosuria.

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/ levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and careers should be made aware that behavioral symptoms of impulse control disorders including pathological gambling, increased libido, hyper sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic

treatments containing levodopa including Carbidopa and Levodopa. Review of treatment is recommended if such symptoms develop.

Concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect. Patients with a history of convulsions should be treated with caution.

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy.

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4.5 Interactions with Other Medicaments

Caution should be exercised when the following drugs are administered concomitantly with Carbidopa and Levodopa '.

Antihypertensive agents

Postural hypotension can occur when Carbidopa and Levodopa ' is added to the treatment of patients already receiving antihypertensive drugs. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants

Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants.

Anticholinergic

Anticholinergic may affect the absorption and thus the patient's response.

Iron

Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate.

Other drugs

To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian drugs.

Dopamine D_2 receptor antagonists (e.g. phenothiazines, butyrophenones, and Risperidone) and isoniazid, may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with Carbidopa and Levodopa ' should be carefully observed for loss of therapeutic response.

Use of Carbidopa and Levodopa ' with dopamine-depleting agents (e.g., tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

Concomitant therapy with Selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone

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

The effect of simultaneous administration of antacids with Carbidopa and Levodopa ' on the bioavailability of levodopa has not been studied.

Carbidopa and Levodopa ' may be given to patients with Parkinson's disease and syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

4.6 Pregnancy and lactation:

Pregnancy

Although the effects of Carbidopa and Levodopa ' on human pregnancy are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Therefore, the use of Carbidopa and Levodopa ' in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Lactation

It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. Because many drugs are

excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue breast-feeding or discontinue the use of Carbidopa and Levodopa ', taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine:

Individual responses to medication may vary and certain side effects that have been reported with Carbidopa and Levodopa ' may affect some patients' ability to drive or operate machinery. Patients treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed 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 and somnolence have resolved.

4.8 Undesirable effects:

Side effects that occur frequently with Carbidopa and Levodopa ' are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by dosage reduction. The most common are dyskinesia including choreiform, dystonic and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

Other side effects reported in clinical trials or in post-marketing experience include:

Body as a whole: syncope, chest pain, anorexia.

Cardiovascular: cardiac irregularities and/or palpitations, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

Gastro-intestinal: vomiting, gastro-intestinal bleeding, development of duodenal ulcer, diarrhoea, dark saliva.

Hematologic: leucopenia, haemolytic and non-haemolytic anemia, thrombocytopenia, agranulocytosis.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura.

Nervous System/Psychiatric: neuroleptic malignant syndrome, Brady kinetic episodes (the "on-off" phenomenon), dizziness, paraesthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion, increased libido. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Respiratory: dyspnoea.

Skin: alopecia, rash, dark sweat.

Urogenital: dark urine.

Rarely convulsions have occurred; however, a causal relationship with Carbidopa and Levodopa ' has not

been established.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with Carbidopa and Levodopa ' include:

Gastro-intestinal: dyspepsia, dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of the tongue.

Metabolic: weight gain or loss, oedema.

Nervous System/Psychiatric: asthenia, decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle cramp, trismus, activation of latent Horner's syndrome, insomnia, anxiety, euphoria, falling and gait abnormalities and Dopamine Dysregulation Syndrome.

Description of selected adverse reactions

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

Impulse control disorders

Pathological gambling, increased libido, hyper sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Carbidopa and Levodopa

Skin: flushing increased sweating.

Special senses: diplopia, blurred vision, dilated pupils, oculogyric crises.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, malignant melanoma.

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose:

Treatment

Management of acute over dosage with Carbidopa and Levodopa ' is basically the same as management of acute over dosage with levodopa; however pyridoxine is not effective in reversing the actions of Carbidopa and Levodopa '. ECG monitoring should be instituted, and the patient carefully observed for

the possible development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as Carbidopa and Levodopa ' should be taken into consideration. To date, no experience has been reported with dialysis, and hence its value in the treatment of over dosage is not known.

The terminal half-life of levodopa is about two hours in the presence of carbidopa.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties:

Pharmacotherapeeutic group: Anti-Parkinson's drugs.

ATC Code: N04BA02

Mechanism of action

Levodopa is a precursor of dopamine, and is given as replacement therapy in Parkinson's disease.

Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of levodopa can be used, reducing the incidence and severity of side effects.

Carbidopa and Levodopa ' is useful in relieving many of the symptoms of Parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhea, and postural instability associated with Parkinson's disease and syndrome.

When response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not controlled evenly throughout the day, substitution of Carbidopa and Levodopa ' usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, Carbidopa and Levodopa ' permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

5.2 Pharmacokinetic Properties:

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastro-intestinal tract. It has a plasma half life of about 1 hour and is mainly converted by decarboxylation to dopamine, a proportion of which is converted to noradrenaline. Up to 30 % is converted to 3-O-methyldopa which has a half life of 9 to 22 hours. About 80 % of levodopa is excreted in the urine within 24 hours mainly as homovanillic acid and dihydroxyphenylactic acid. Less than 1% is excreted unchanged.

Once in the circulation it competes with other neutral amino acids for transport across the blood brain barrier.

Once it has entered the striatal neurones it is decarboxylated to dopamine, stored and released from presynaptic neurones. Because levodopa is so rapidly decarboxylated in the gastro-intestinal tract and the liver, very little unchanged drug is available for transport into the brain. The peripheral decarboxylation reduces the therapeutic effectiveness of levodopa but is responsible for many of its side effects. For this reason levodopa is usually administered together with a peripheral decarboxylase inhibitor such as carbidopa, so that lower doses may be given to achieve the same therapeutic effect.

Carbidopa in the absence of levodopa, is rapidly but incompletely absorbed from the gastrointestinal tract following oral dosing. Following an oral dose approximately 50% is recorded in the urine, with about 3% of this as unchanged drug. It does not cross the blood brain barrier but crosses the placenta and is excreted in breast milk. Turnover of the drug is rapid and virtually all unchanged drug appears in the urine within 7 hours.

Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine but as it does not cross the blood brain barrier, effective brain levels of dopamine get produced with lower levels of levodopa therapy reducing the peripheral side effects, noticeably nausea and vomiting and cardiac arrhythmias.

6. Pharmaceutical Particulars

6.1 List of excipients:

Citric acid monohydrate

Disodium edetate

Sodium Metabisulphite

Microcrystalline cellulose

Ethyl cellulose

Povidone

Colloidal anhydrous silica

Croscarmellose sodium

Talc

Magnesium stearate

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 Months from the date of Manufacturing.

6.4 Special precautions for storage:

Store below 25°C. Keep medicine away from the reach of children

6.5 Nature and contents of container:

Alu/Alu Pack of 10 Tablets

7. Marketing Authorization Holder:

Micro Labs Limited

31, race course road

Bangalore-560001

INDIA

MICRO NOVA PHARMACEUTICALS IND LTD,
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8. Marketing Authorization Numbers

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9. Date of first authorization

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10. Date of revision of the text

May 2021