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INSTRUCTION
for medical use
CONFUNDUS®

Composition:
active substances: carbidopa, levodopa.
Each tablet contains carbidopa monohydrate equivalent to carbidopa 25 mg, levodopa 250 mg;
excipients: pregelatinized starch, microcrystalline cellulose, crospovidone, hydroxyl propyl cellulose, magnesium stearate.

Pharmaceutical form. Tablets.
Main physical and chemical properties: white to off-white butterfly-shaped flat tablets, with a deep score line on one side and a normal score line on the other side.

Pharmacotherapeutic group. Anti-Parkinson drugs. Dopaminergic agents. DOPA and its derivatives. Levodopa and decarboxylase inhibitor.
ATC code: N04B A02.

Pharmacological properties.
Pharmacodynamics.
Confundus® is a combined anti-Parkinson agent containing the metabolic precursor of dopamine, levodopa, used as a replacement therapy for Parkinson's disease/syndrome, and a peripheral dopa decarboxylase inhibitor, carbidopa, which inhibits the metabolism of levodopa, that enters the brain and is converted there to dopamine.
This combination makes it possible to use a lower dose of levodopa, which reduces the frequency and severity of side effects.
The combination of carbidopa/levodopa helps to relieve many symptoms of Parkinson's disease/syndrome, especially rigidity and bradykinesia. This combination is frequently helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability.
When clinical response to levodopa alone is irregular, and objective and subjective symptoms of Parkinson's disease are not controlled evenly throughout the day, taking carbidopa/levodopa usually reduces fluctuations in therapeutic response.
By reducing some of the adverse reactions produced by levodopa alone, its use in combination with carbidopa permits more patients to obtain adequate relief from the symptoms of Parkinson's disease/syndrome.
Pharmacokinetic properties.

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastrointestinal tract. It has a plasma half life of about 1 hour and is mainly metabolized 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 neurons it is decarboxylated to dopamine, stored and released from presynaptic neurons. Because levodopa is so rapidly decarboxylated in the gastrointestinal 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. Approximately 50% is recorded in the urine, with about 3% of this as unchanged drug.
Carbidopa 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, vomiting and cardiac arrhythmias.

Clinical particulars.
Indications.
- Parkinson's disease.
- Parkinson's syndrome.

Contraindications.
- Hypersensitivity to the active substances or to any of the excipients of the drug.
- Concomitant use of non-selective monoamine oxidase inhibitors (MAO) (these drugs should be discontinued at least two weeks before treatment with Confundus®). The drug can be used only with selective MAO-B inhibitors in the recommended doses (e.g., selegiline hydrochloride).
- Angular glaucoma.
- Suspicious (for melanoma) pigmented neoplasms on the skin or a history of melanoma.
- Severe psychosis.
- Pregnancy.
- Breastfeeding.

Interaction with other medicinal products and other forms of interaction.
Caution should be exercised when the following drugs are administered concomitantly with carbidopa/levodopa.
Antihypertensive agents.
Postural hypotension can occur when carbidopa/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 (see “Contraindications” section).
Anticholinergics.
Anticholinergics 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 anti-Parkinson drugs.
Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, and risperidone) and isoniazid, may reduce the therapeutic effects of levodopa. Patients should be carefully observed for loss of anti-Parkinson effect.
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/levodopa should be carefully observed for loss of therapeutic response.
Use of carbidopa/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 (see “Contraindications” section).
Since levodopa competes with certain amino acids, the absorption of the drug may be impaired in some patients on a high protein diet.
The effect of simultaneous administration of antacids with carbidopa/levodopa on the bioavailability of levodopa has not been studied.
The drug may be given to patients with Parkinson's disease/syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

Special warnings and precautions for use.
General.
Carbidopa/levodopa is not recommended for the treatment of drug-induced extrapyramidal reactions.
Carbidopa/levodopa should be administered cautiously to patients with bronchial asthma, cardiovascular disease, pulmonary disease, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastrointestinal hemorrhage).
Patients with a history of convulsions should be treated with caution.
As Confundus® contains levodopa, periodic evaluation of hepatic, renal, cardiovascular, and hematopoetic function are recommended during extended therapy.
Cardiac arrhythmias.
Care should be exercised when carbidopa/levodopa is administered to patients with a history of myocardial infarction who have residual sinoatrial or ventricular arrhythmias. Cardiac function should be closely monitored with particular care in such patients during the period of initial dosage adjustment.
Somnolence and sudden sleep onset.
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.

Dyskinesia.
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.
Mental disorders.
All patients receiving carbidopa/levodopa therapy 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.
As Confundus® contains 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 Confundus® is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Confundus® may cause a recurrence.
Neuroleptic malignant syndrome.
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 anti-Parkinson agents. Therefore, any abrupt dosage reduction or withdrawal of Confundus® should be carefully observed, particularly in patients who are also receiving neuroleptics.
Dopamine Dysregulation Syndrome (DDS).
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 (see also "Adverse reactions" section).
Impulse control disorders.
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, 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 Confundus®. Review of treatment is recommended if such symptoms develop.
Glaucoma.
Patients with chronic wide-angle glaucoma may be treated cautiously with carbidopa/levodopa, provided the intra-ocular pressure is well controlled and the patient monitored carefully for changes in intra-ocular pressure during therapy.
Anaesthesia.
If general anaesthesia is required, therapy with carbidopa/levodopa 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 may be restarted as soon as oral medication can be taken at the same daily dosage as before.
Melanoma.
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 for any indication. Ideally, periodic skin examinations should be performed by dermatologist.
Laboratory tests.
Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa/levodopa than with levodopa alone. Transient metabolic abnormalities include

elevated levels of blood urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), bilirubin, and alkaline phosphatase.
Decreased hemoglobin, hematocrit, elevated serum glucose and white blood cells, bacteria and red blood cells in the urine have been reported.
Positive Coombs' tests have been reported, both with carbidopa/levodopa and levodopa alone.
Carbidopa/levodopa 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.

Use during pregnancy or breastfeeding.
Pregnancy.
Although the effects of carbidopa/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 Confundus® in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.
Breastfeeding.
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 Confundus®, taking into account the importance of the drug to the mother.
Effects on the ability to drive and use machines.
Individual responses to carbidopa/levodopa may vary and certain side effects that have been reported with Confundus® 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 (see “Special warnings and precautions for use” section).

Administration and dosage.
The drug should be taken orally.
Confundus® contains carbidopa and levodopa in a ratio of 1:10 (25 mg / 250 mg); these tablets are taken whole. As the tablet can not be divided, if it is necessary to prescribe carbidopa/levodopa at a dose of 12.5 mg / 125 mg, drugs with these active ingredients should be used with the possibility of such a dosage.
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.
For patients initiating Confundus® therapy, the starting dose of carbidopa/levodopa should be 12.5 mg / 125 mg once or twice daily.
If necessary, the dose of carbidopa/levodopa can be gradually increased by another 12.5 mg / 125 mg daily or by 25 mg / 250 mg every other day until the optimal therapeutic effect is obtained.
The therapeutic effect 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. are reached within seven days as compared to weeks or months with levodopa alone.
Patients receiving levodopa.
Discontinue levodopa at least 12 hours (24 hours for slow-release preparations) before starting therapy with Confundus®.

The daily dose of Confundus® should be approximately 20% of the previous daily dosage of levodopa.
Initial dosing.
For patients who are taking less than 1500 mg of levodopa per day, the initial daily dose should be 75–100 mg of carbidopa and 300–400 mg of levodopa in 3 or 4 doses (use a drug with a ratio of carbidopa/levodopa 1:4).
For patients receiving more than 1500 mg of levodopa per day, the initial dose of Confundus® should be 1 tablet 3 or 4 times a day.
Maintenance.
Therapy with Confundus® should be individualized and adjusted gradually according to response. When more levodopa is required, the dose of carbidopa/levodopa can be increased by another 12.5 mg / 125 mg daily or by 25 mg / 250 mg every other day to the maximum daily dose of 200 mg carbidopa and 2 g levodopa (8 tablets for 3–4 doses) for patients with a body weight of 70 kg.
Patients receiving levodopa with another decarboxylase inhibitor. When transferring a patient to combination drug Confundus® from levodopa is combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before therapy is started. Begin Confundus® with a dosage that will provide the same amount of levodopa as contained in the other levodopa/decarboxylase inhibitor combination.
Patients receiving other anti-Parkinson agents. The combination of Confundus® with monoamine oxidase-B (MAO-B) inhibitors may increase the effectiveness of the drug in controlled cases of akinesia and/or dyskinesia.
Patients who are taking other anti-Parkinson medicines at the same time as Confundus® may need to adjust the dose of these medicines.
Elderly patients.
This product is used in elderly patients.
Children.
The safety and efficacy of the drug in children have not been established, so it is not recommended for use in patients under 18 years of age.

Overdose.
Management of acute overdosage with carbidopa/levodopa is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of Confundus® ingredients. 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/levodopa should be taken into consideration. To date, no experience has been reported with dialysis, and hence its value in the treatment of overdosage is not known. The terminal half-life of levodopa is about two hours in the presence of carbidopa.

Adverse reactions.
Adverse reactions that occur frequently with carbidopa/levodopa drugs are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by dosage reduction. The most common are dyskinesias including choreiform, dystonic and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.
Immune system disorders: hypersensitivity reactions, including angioneurotic edema, urticaria, pruritus, Schoenlein–Henoch disease.
Skin and subcutaneous tissue disorders: alopecia, rash, dark sweat, redness, sweating, melanoma.
Blood and lymphatic system disorders: leukopenia, anemia, hemolytic anemia, thrombocytopenia, agranulocytosis.

Cardiovascular system disorders: cardiac arrhythmias and/or palpitations, orthostatic effects, including episodes of hypotension, hot flashes, hypertension, phlebitis, chest pain.
Respiratory system disorders: dyspnea, respiratory disorders, hoarseness.
Gastrointestinal tract disorders: vomiting, gastrointestinal bleeding, duodenal ulcer, diarrhea, dark saliva, dyspepsia, dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain, constipation, flatulence, burning sensation of the tongue.
Urinary system disorders: dark urine, urinary retention, urinary incontinence, priapism.
Eye disorders: diplopia, blurred vision, dilated pupils, oculogyric crises.
Metabolic disorders: weight gain or loss, edema.
Benign, malignant and unspecified neoplasms (including cysts and polyps): melanoma (see "Contraindications" and "Special warnings and precautions for use" sections).
Nervous system disorders: dyskinesias including choreiform, dystonic and other involuntary movements; blepharospasm, headache, syncope, neuroleptic malignant syndrome (see "Contraindications" section); bradykinetic episodes (the "on-off" phenomenon); dizziness; paresthesias; sleep disorders, including drowsiness, excessive daytime sleepiness, and episodes of sudden sleep onset; convulsions; asthenia, ataxia, numbness, increased hand tremor, muscle twitching, trismus, activation of latent Horner's syndrome, insomnia, falls, gait disturbances, dopamine dysregulation syndrome[1].
Mental disorders: anorexia, dysphoria, episodes of psychosis (including delusions, hallucinations and paranoid thoughts); depression with or without development of suicidal tendencies; dementia; agitation; irritation, confusion; increase libido; decreased sharpness of thinking, disorientation, anxiety, euphoria, Impulse control disorders[2].
Others: general weakness, pathological fatigue.

[1] 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 "Special warnings and precautions for use" section).

[2] Impulse control disorders.
Pathological gambling, increased libido, hypersexuality, 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 Sinemet (see "Special warnings and precautions for use" section).

Shelf life.
2 years.

Storage conditions.
Store in original package at temperature below 25°C.
Keep out of reach of children.

Package.
10 tablets in a blister; 10 blisters in a carton pack.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision.