SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Confundus 25 mg/250 mg (Carbidopa and Levodopa) Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains.
Carbidopa BP….25 mg.
Levodopa BP….250 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White to off white butterfly shape flat tablet, deep break line on one side and normal break line on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antiparkinsonian agent.
For treatment of Parkinson's disease and syndrome.

4.2 Posology and method of administration

Route of administration: Oral

General Considerations:
Confundus is used in adults orally. The optimal daily dose of the drug should be carefully selected for each patient.

Patients not receiving levodopa:
For patients starting treatment with Confundus, the initial dose is 1/2 tablets once or twice daily after a meal. If necessary, increase the dose by gradual addition of 1/2 tablets daily or alternate day till optimal therapeutic effect is obtained.

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.

Patients receiving levodopa:
Levodopa should be stopped for at least 12 hours (24 hours for slow release) before starting treatment with Confundus. The easiest way is to take the drug in the morning, and at the same time do not use levodopa. The dose of the drug should contain approximately 20% of the previous daily dose of levodopa.

Initial dose: Patients who receive more than 1500 mg levodopa per day should start with a dose of 1 tablet 3-4 times a day.

Supportive therapy: Confundus therapy should be individualized and adjusted gradually according to the therapeutic effect.

If necessary, the dose of the drug can be increased to 1 tablet 3-4 times a day. If necessary, the dose of the drug can be increased by 1 tablet per day or on alternate day. The maximum daily dose of Confundus is 8 tablets (200 mg carbidopa and 2 g levodopa).

Patients receiving other decarboxylase inhibitors:
When a patient is switched from a combination of levodopa to other decarboxylase inhibitors, the use of these drugs should be stopped 12 hours prior to the start of the drug Confundus. It is necessary to begin with the dosage of the drug Confundus, which will provide the same amount of levodopa as in the combination of levodopa / other inhibitors of decarboxylase.

Patients receiving other anti-parkinsonian drugs:
Other anti-parkinsonian agents may be continued when Confundus is introduced, although their dose should be adjusted by a physician in accordance with instructions for medical use.

Use in children:
The safety of 'Confundus' in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

Elderly patients:
This drug is used in elderly patients.

4.3 Contraindications

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with 'Confundus'. These inhibitors must be discontinued at least two weeks before starting 'Confundus'. 'Confundus' may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegiline hydrochloride). (See section 4.5)
'Confundus' 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. See also section 4.6.

4.4 Special warnings and precautions for use

'Confundus' is not recommended for the treatment of drug-induced extrapyramidal reactions. 'Confundus' 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 haemorrhage).
Care should be exercised when 'Confundus' 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, 'Confundus' 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. 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 'Confundus' should be carefully observed, particularly in patients who are also receiving neuroleptics.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioral 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.

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 'Confundus', 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 'Confundus' 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, 'Confundus' 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 'Confundus' 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 combination of levodopa and carbidopa than with levodopa alone. 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 urinehave been reported.

Positive Coombs' tests have been reported, both with combination of levodopa and carbidopa and levodopa alone.
'Confundus' 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.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with 'Confundus'.

Antihypertensive agents
Postural hypotension can occur when 'Confundus' 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 first paragraph of section 4.3 for patients receiving MAOIs).

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 antiparkinsonian drugs.
Dopamine D2 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 'Confundus' should be carefully observed for loss of therapeutic response.

Use of 'Confundus' 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 4.3 'Contraindications')
Since levodopa competes with certain amino acids, the absorption of 'Confundus' may be impaired in some patients on a high protein diet.
The effect of simultaneous administration of antacids with 'Confundus' on the bioavailability of levodopa has not been studied.

'Confundus' 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 'Confundus' 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.

Breast-feeding mothers

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.

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary and certain side effects that have been reported with 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 (see also section 4.4 'Special warnings and precautions for use').

4.8 Undesirable effects

Side effects that occur frequently with 'Confundus' 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.

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.

Haemotologic: leucopenia, haemolytic and non-haemolyticanaemia, thrombocytopenia, agranulocytosis.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonleinpurpura.

Nervous System/Psychiatric: neuroleptic malignant syndrome (see 4.3 'Contraindications'), bradykinetic 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 'Confundus' has not been established.
Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with 'Confundus' include:

Gastro-intestinal: dyspepsia, dry mouth, bitter taste, sialorrhoea, 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.

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 Confundus (see section 4.4. 'Special warnings and precautions for use')

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 (see 4.3 'Contraindications').

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Management of acute overdosage with 'Confundus' is basically the same as management of acute over dosage with levodopa; however pyridoxine is not effective in reversing the actions of 'Confundus'. 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 'Confundus' 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

'Confundus' is useful in relieving many of the symptoms of parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhoea, 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 'Confundus' usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, 'Confundus' 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 to22 hours. About 80 % of levodopa is excreted in the urine within 24 hours mainly as homovanillic acid and di-hydroxyphenyl lactic 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.

5.3 Preclinical safety data

'Confundus' is well established in medical use. Preclinical data is broadly consistent with clinical experience. (For reproductive toxicity, see section 4.6)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized starch, Microcrystalline cellulose (Avicel PH101), Crospovidone XL, Hydroxyl propyl cellulose L, Purified water, Microcrystalline cellulose (Avicel PH102), Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store below 30°C. Protect from light.
Keep all medicines out of reach of children.

6.5 Nature and contents of container

Alu/Alu blister pack of 10 tablets. Such 3 blisters are packed in a carton along with packaging insert.

6.6 Special precautions for disposal and other handling

None

7. MARKETING AUTHORISATION HOLDER

Kusum Healthcare Pvt. Ltd.,
SP 289 (A), RIICO Industrial area,
Chopanki, Bhiwadi (Rajasthan), India

8. MARKETING AUTHORISATION NUMBER(S)

04978/07278/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

07 August 2020

10. DATE OF REVISION OF THE TEXT

08/2023

11. REFERENCES

SmPC published on electronic medicines compendium
https://www.medicines.org.uk/emc#gref

The MHRA published product information
https://products.mhra.gov.uk/

Human medicine European public assessment report
https://www.ema.europa.eu/en/medicines