Date of submission: 19 August 2022
Approved: 31 October 2022

Proposed Professional Information for LECARDOP 25/250 and 25/100 (Clean Copy)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LECARDOP 25/250 tablets

LECARDOP 25/100 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of LECARDOP 25/250 contains:

Levodopa: 250 mg

Carbidopa: 25 mg

Each tablet of LECARDOP 25/100 contains:

Levodopa: 100 mg

Carbidopa: 25 mg

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

LECARDOP 25/250: Mottled blue to light blue coloured oval shaped, biconvex, uncoated tablets

debossed with “519” on one side and scored on the other side.

LECARDOP 25/100: Yellow to light yellow coloured oval shaped, biconvex, uncoated tablets debossed with “518” on one side and scored on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LECARDOP is indicated for the treatment of Parkinson’s disease and syndrome, to relieve rigidity and bradykinesia and may be helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability associated with Parkinson’s disease and syndrome.

4.2 Posology and method of administration

General considerations:

Take LECARDOP on an empty stomach (see section 4.5).

Dosage should be titrated to the individual patient’s needs and this may require adjusting both individual dose and the frequency of administration.

Standard anti-parkinsonism medicines, other than levodopa alone, may be continued while LECARDOP is being administered, although their dosage may have to be adjusted.

If general anaesthesia is required, LECARDOP may be continued, as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

Usual initial dosage:

Dosage is best initiated with one tablet of LECARDOP 25/100 three times a day. This dosage

schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet every day, or every other day, as necessary until the dosage equivalent of eight tablets of LECARDOP 25/100 per day is reached.

For patients starting with LECARDOP 25/250, the initial dose is half a tablet taken once or twice daily. However, this may not provide the optimal amount of carbidopa needed by many patients. If necessary, add half a tablet every day or every other day until optimal response 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.

How to transfer patients from levodopa:

Because both therapeutic and adverse responses occur more rapidly with LECARDOP than when levodopa is given alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with LECARDOP than with levodopa alone. The occurrence of involuntary movements may require dosage reduction.

Blepharospasm may be a useful early sign of excess dosage in some patients.

Levodopa must be discontinued at least 12 hours before LECARDOP is started (this should be 24 hours for slow-release preparations of levodopa). A daily dosage of LECARDOP should be chosen that will provide approximately 20 % of the previous levodopa daily dosage.

Patients who are taking less than 1 500 mg levodopa a day should be started on one tablet of LECARDOP 25/100 three or four times daily. The suggested starting dosage for most patients taking more than 1 500 mg levodopa is one tablet of LECARDOP 25/250 three or four times a day.

Maintenance:

Treatment with LECARDOP should be individualised and adjusted gradually according to response.

At least 70 to 100 mg of carbidopa per day should be provided for optimal inhibition of extra-cerebral decarboxylation of levodopa. When more levodopa is required, LECARDOP 25/250 should be substituted for LECARDOP 25/100. If necessary, the dosage of LECARDOP 25/250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Maximum recommended dose:

Eight tablets of LECARDOP 25/250 per day (200 mg of carbidopa and 2 g of levodopa). This is approximately 3 mg/kg of carbidopa and 30 mg/kg of levodopa in a patient weighing 70 kg.

Paediatric use:

Safety and efficacy in paediatric patients have not been established.

Use of LECARDOP in patients below the age of 18 is not recommended.

4.3 Contraindications

- Known hypersensitivity to levodopa, carbidopa or any component of LECARDOP listed in section 6.1.
- Narrow-angle glaucoma.
- Undiagnosed skin lesion or a history of melanoma (since levodopa is known to activate a malignant melanoma).
- Pregnancy and lactation (see section 4.6).
- Severe psychosis.

- Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with LECARDOP. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with LECARDOP. LECARDOP may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B (e.g. selegiline HCl) (see section 4.5).

4.4 Special warnings and precautions for use

LECARDOP is not recommended for the treatment of medicine-induced extrapyramidal reactions.

LECARDOP may be given to patients already receiving levodopa alone, however, the levodopa alone must be discontinued at least 12 hours before LECARDOP is started. LECARDOP should be substituted at a dosage that will provide approximately 20 % of the previous levodopa dosage (see section 4.2).

Dyskinesia 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 dyskinesia may require dosage reduction.

Monoamine oxidase (MAO) inhibitors must be discontinued at least 2 weeks prior to initiation of LECARDOP therapy (see section 4.3).

LECARDOP should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, a history of peptic ulcer disease (because of the possibility of upper gastrointestinal haemorrhage) or convulsions.

Caution is advised when LECARDOP is administered to patients with a history of myocardial

infarction, who have residual atrial, nodal, or ventricular dysrhythmias. Cardiac function should be monitored, with particular care in such patients during the period of initial dosage administration and titration.

Periodic evaluations of hepatic, haematopoietic, cardiovascular and renal function are recommended during therapy with LECARDOP. The occurrence of blepharospasm is a sign of over-dosage with LECARDOP.

Neuroleptic malignant syndrome (NMS) is an uncommon but life-threatening syndrome characterised by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes, other disturbances, such as autonomic dysfunction, tachycardia, tachypnoea, sweating, hyper- or hypotension; laboratory findings such as creatine phosphokinase elevation, leucocytosis, myoglobinuria and increased myoglobinuria have been reported.
The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g. pneumonia, systemic infection) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequate treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported when anti-Parkinson medicines were withdrawn abruptly.
Therefore, patients should be observed carefully when the dosage of LECARDOP is reduced

abruptly or discontinued, especially if the patient is receiving neuroleptics.

Caution is advised when treating patients with chronic wide-angle glaucoma. Patients should only receive treatment with LECARDOP if intraocular pressure is well controlled and the patient is carefully monitored for changes in intraocular pressure during treatment.

Patients with Parkinson's disease have a higher risk of developing melanoma. It is unclear whether the increased risk is observed due to Parkinson's disease or other factors, such as medicines used to treat Parkinson's disease. Periodic skin examinations should be performed by appropriately qualified professionals (e.g. dermatologists), and patients and caretakers are advised to monitor for melanomas.

LECARDOP may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine levels following the administration of levodopa, and the use of LECARDOP may cause a recurrence. Patients with a history of severe involuntary movements or psychotic episodes should be closely monitored. Dosage reductions may be required. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies and antisocial behaviour. Patients with past or current psychoses should be treated with caution. Caution should be exercised with concomitant administration of psychoactive medicines and LECARDOP (see section 4.5).

Patients should be regularly monitored for the development of impulse control disorders. Behavioural symptoms of impulse control disorders include pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating. Review of treatment is recommended if such symptoms develop.

Concomitant administration of psychoactive medicines, such as phenothiazines or butyrophenones, should be done with caution and the patient should be carefully observed for loss of antiparkinsonian effect (see section 4.5).

Patients with a history of convulsions should be treated with caution.

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 section 4.8).

Laboratory tests:
Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of LECARDOP 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 LECARDOP and levodopa alone.

LECARDOP 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 medicines and other forms of interaction

The following medicines may interact with LECARDOP:

Antihypertensive medicines

Symptomatic postural hypotension occurred when LECARDOP was added to the treatment of a patient receiving antihypertensive medicines. Therefore, when therapy with LECARDOP is initiated, dosage adjustment of the antihypertensive medicine may be required.

Antidepressants

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see section 4.3).

There have been reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and LECARDOP (see section 4.3 for patients receiving MAO inhibitors).

Iron salts

Iron salts may reduce the bioavailability of levodopa and carbidopa.

Other medicines:

- **Metoclopramide** may increase the bioavailability of levodopa by increasing gastric emptying. Metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.
- **Anticholinergic medicine** (such as orphenadrine, trihexyphenidyl, benzatropine and procyclidine). There have been reports of high blood pressure or involuntary body movements, when LECARDOP was combined with a tricyclic antidepressant.

- **Phenytoin, papaverine, haloperidol and isoniazid** will decrease the effectiveness of LECARDOP.
- **Dopamine D_2 receptor agonists** (such as phenothiazines, butyrophenones and risperidone) may reduce the therapeutic effects of levodopa (see section 4.4).
- **A high protein diet**. Levodopa, as in LECARDOP, competes with certain amino acids and a high protein diet may impair the absorption of levodopa.
- **Dopamine-depleting medicines** (e.g. reserpine and tetrabenazine). Concomitant use with LECARDOP or other medicines known to deplete monoamine stores, is not recommended.

The effect of simultaneous administration of antacids with LECARDOP on the bioavailability of levodopa has not been studied.

LECARDOP 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

Safety and efficacy in pregnancy have not been established. Combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see section 4.3).

Lactation

LECARDOP is excreted in breast milk.

Women using LECARDOP should not breastfeed their infants (see section 4.3).

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

Sudden onset of sleep during daily activities, in some cases without warning signs, somnolence and dizziness, which may affect the ability to drive a vehicle and operate machinery, may occur. Caution is advised before driving a vehicle or operating machinery until the effects of LECARDOP are known. Patients who have experienced somnolence and/or an episode of sudden sleep onset must not drive a vehicle or operate machinery.

4.8 Undesirable effects

Side effects that occur frequently in patients receiving LECARDOP are those due to the central neuropharmacologic activity of dopamine.

These reactions usually can be diminished by dosage reduction. The most common side effects 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 serious side effects reported in clinical trials or in post-marketing experience include:

Neoplasm benign, malignant and unspecified (including cysts and polyps)

Less frequent: Malignant melanoma.

Blood and lymphatic system disorders

Less frequent: Agranulocytosis, leukopenia, haemolytic and non-haemolytic anaemia and thrombocytopenia.

Immune system disorders

Less frequent: Angioedema.

Metabolism disorders

Frequent: Anorexia.

Less frequent: Weight loss and weight gain.

Psychiatric disorders

Frequent: Confusion, depression with or without suicidal tendencies, dream abnormalities, hallucinations and insomnia.

Less frequent: Agitation, anxiety, disorientation, bruxism, dementia, euphoria, increased libido, psychotic episodes including delusions and paranoid ideation.

Frequency unknown: Dopamine dysregulation syndrome.

Nervous system disorders

Frequent: Dyskinesias, bradykinetic episodes (the “on-off” phenomenon), dizziness, dystonia, headache and paraesthesia.

Less frequent: Chorea, decreased mental acuity, extrapyramidal and movement disorders, falling, gait abnormalities, somnolence including very rarely excessive daytime somnolence and sudden sleep onset episodes, syncope, activation of latent Horner's syndrome, ataxia, convulsions, faintness, increased hand tremor, numbness, oculogyric crises, sense of stimulation and trismus.

Eye disorders

Less frequent: Diplopia, blepharospasm, blurred vision and dilated pupils.

Cardiac disorders

Less frequent: Palpitation and cardiac irregularities.

Vascular disorders

Frequent: Orthostatic effects including hypotensive episodes.

Less frequent: Flushing, hot flashes, hypertension and phlebitis.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Less frequent: Bizarre breathing patterns and hoarseness.

Gastrointestinal disorders

Frequent: Constipation, diarrhoea, dry mouth, dyspepsia, nausea and vomiting.

Less frequent: Gastrointestinal pain, bitter taste, burning sensation of the tongue, dark saliva, development of duodenal ulcer,-dysphagia, flatulence, gastrointestinal bleeding, hiccups, and sialorrhoea.

Skin and subcutaneous tissue disorders

Less frequent: increased sweating, urticaria, alopecia, dark sweat, Henoch-Schönlein's purpura, pruritus and rash.

Musculoskeletal and connective tissue disorders

Frequent: Muscle cramps.

Less frequent: Muscle twitching.

Renal and urinary disorders

Less frequent: Dark urine, urinary incontinence and urinary retention.

Reproductive system and breast disorders

Less frequent: Priapism.

General disorders and administration site conditions

Less frequent: Asthenia, malaise, oedema, fatigue, neuroleptic malignant syndrome (see section 4.4) and weakness.

Investigations

Less frequent: Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with LECARDOP. These include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, creatinine, uric acid and positive Coombs test.

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

Description of selected adverse reactions

Dopamine dysregulation syndrome (DDS):

DDS is an addictive disorder seen in some patients treated with carbidopa/levodopa. Affected patients show a compulsive pattern of dopaminergic medicine 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 (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying and binge/compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa, including LECARDOP (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LECARDOP is important. It allows continued monitoring of the benefit/risk balance of LECARDOP. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

See section 4.8.

Overdose of LECARDOP can cause blepharospasm and an uneven heart rate.

Treatment

Since there is no antidote for acute overdose of LECARDOP, treatment is symptomatic and supportive.

Pyridoxine is not effective in reversing the actions of LECARDOP.

General supportive measures should be employed, along with activated charcoal. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of dysrhythmias; if required, appropriate antidysrhythmic therapy should be given.

The possibility that the patient may have taken other medicines as well as LECARDOP should be taken into consideration. To date, no experience has been reported with dialysis; hence its value in 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

Category and class: A 5.4.1 Anti-Parkinsonism preparations

Pharmacotherapeutic group: Levodopa: dopaminergics; carbidopa: dopadecarboxylase inhibitor.

ATC code: N04BA02.

LECARDOP is an immediate release tablet containing a combination of carbidopa and levodopa.

Levadopa is a metabolic precursor of dopamine. When levodopa is administered orally it is rapidly decarboxylated to dopamine in extra-cerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system.

Carbidopa is an inhibitor of dopa decarboxylase present in peripheral tissue. Its administration with levodopa prevents peripheral decarboxylation of levodopa. Thus, this combination reduces the amount of levodopa required by about 75 % and increases both plasma levels and the half-life of levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

5.2 Pharmacokinetic properties

Levodopa is rapidly, but variably absorbed from the gastrointestinal tract after oral administration in the absence of a decarboxylase inhibitor. The plasma half-life of levodopa is approximately 1 hour.

Up to 30 % of levodopa is converted to 3-*O*-methyldopa, which has a half-life of 9 – 22 hours. Approximately 80 % of levodopa is excreted in the urine within 24 hours, mainly as homovanillic acid and dihydroxyphenylacetic acid. Less than 1 % of the administered dose is excreted unchanged.

Carbidopa is rapidly but incompletely absorbed from the gastrointestinal tract after oral administration in the absence of levodopa. Approximately 50 % of the administered dose is excreted in the urine, with approximately 3 % as unchanged parent compound which appears within 7 hours.

Elimination half-life of levodopa in the presence of carbidopa is about 1,5 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch/maize starch

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Sodium starch glycolate

D&C Yellow no. 10 aluminium lake (LECARDOP 25/100)

FD&C Yellow no. 6 aluminium lake (LECARDOP25/100)

FD&C Blue no. 2 aluminium lake (LECARDOP 25/250).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light. Keep the bottle tightly closed.

6.5 Nature and contents of container

LECARDOP tablets are packed into HDPE, white, smooth, round bottles with a white ribbed child-resistant cap, embossed with a pictorial design on top. The bottle is packed in a printed outer carton.

Pack size: 100 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1, Roodepoort

Johannesburg 1724

8. REGISTRATION NUMBERS

LECARDOP 25/250: 45/5.4.1/0764

LECARDOP 25/100: 45/5.4.1/0765

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2016

10. DATE OF REVISION OF THE TEXT

31 October 2022