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

Professionele Inligting vir LECARDOP 25/250 en 25/100

SKEDULERINGSTATUS

S4

1. NAAM VAN DIE MEDISYNE

LECARDOP 25/250 tablette

LECARDOP 25/100 tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke tablet van LECARDOP 25/250 bevat:

Levodopa: 250 mg

Karbidopa: 25 mg

Elke tablet van LECARDOP 25/100 bevat:

Levodopa: 100 mg

Karbidopa: 25 mg

Suikervry.

Vir die volledige lys van onaktiewe bestanddele, sien afdeling 6.1.

3. FARMASEUTIESE VORM

Tablette.

LECARDOP 25/250: Gespikkelde blou- tot ligblougekleurde ovaalvormige, bikonvekse, onbedekte tablette gepers met “519” op een kant en gekeep op die ander kant.
LECARDOP 25/100: Geel- tot liggeelgekleurde ovaalvormige, bikonvekse, onbedekte tablette gepers met “518” op een kant en gekeep op die ander kant.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

LECARDOP word aangedui vir die behandeling van Parkinson se siekte en sindroom, om rigiditeit en bradikinesie te verlig en mag help om tremor, disfagie, sialorree en posturale onstabiliteit geassosieer met Parkinson se siekte en sindroom te beheer.

4.2 Posologie en metode van toediening

Algemene oorwegings:

Neem LECARDOP op ‘n leë maag (sien afdeling 4.5).

Dosering moet getitreer word volgens die individuele pasiënt se behoeftes en dit mag vereis dat sowel die individuele dosis as die frekwensie van toediening aangepas word.

Standaard antiparkinsonisme medisyne, buiten levodopa alleen, kan voortgesit word terwyl LECARDOP toegedien word, alhoewel dit nodig mag wees om die dosis daarvan aan te pas.

Indien algemene narkose nodig is, mag LECARDOP volgehou word, vir so lank as wat die pasiënt toegelaat word om vloeistowwe en medikasie per mond in te neem. Indien terapie tydelik onderbreek is, kan die gewone daaglikse dosis toegedien word sodra die pasiënt in staat is om mondelikse medikasie te neem.

Normale aanvanklike dosering:

Dit is die beste om dosering te begin met een tablet LECARDOP 25/100 drie keer ‘n dag. Hierdie doseringskedule lewer 75 mg karbidopa per dag. Dosering kan verhoog word met een tablet elke dag, of elke tweede dag, soos wat nodig is, totdat die dosering gelykstaande aan agt tablette LECARDOP 25/100 per dag bereik word.

Vir pasiënte wat begin met LECARDOP 25/250, is die aanvanklike dosis ‘n halwe tablet een of twee keer per dag geneem. Dit mag egter nie die optimale hoeveelheid karbidopa verskaf wat deur baie pasiënte benodig word nie. Indien nodig, voeg ‘n halwe tablet elke dag of elke tweede dag by totdat die optimale respons verkry word.

‘n Respons is binne ‘n dag waargeneem, en soms na een dosis. Ten volle effektiewe dosisse word gewoonlik binne sewe dae bereik, in vergelyking met weke of maande met levodopa alleen.

Hoe om pasiënte vanaf levodopa oor te skakel:

Omdat sowel terapeutiese as ongunstige reaksies meer dikwels met LECARDOP voorkom as wanneer levodopa alleen gegee word, moet pasiënte noukeurig gemoniteer word tydens die tydperk wat die dosis aangepas word. Onwillekeurige bewegings sal spesifiek vinniger met LECARDOP voorkom as met levodopa alleen. Dit mag nodig wees om die dosis te verlaag indien onwillekeurige bewegings voorkom.
Blefarospasma kan by sommige pasiënte ‘n nuttige vroeë teken wees dat die dosis te hoog is.

Levodopa moet ten minste 12 uur voordat met LECARDOP begin word, gestaak word (dit moet 24 uur wees vir stadige-vrystellingspreparate van levodopa). Kies ‘n daaglikse dosis LECARDOP wat ongeveer 20 % van die vorige daaglikse dosis levodopa sal verskaf.

Pasiënte wat minder as 1 500 mg levodopa per dag neem, moet terapie begin met een tablet LECARDOP 25/100 drie of vier keer daagliks. Die voorgestelde aanvangsdosering vir die meeste pasiënte wat meer as 1 500 mg levodopa neem, is een tablet of LECARDOP 25/250 drie of vier keer ‘n dag.

Instandhouding:

Behandeling met LECARDOP moet geïndividualiseer en geleidelik aangepas word na gelang van die respons.

Ten minste 70 tot 100 mg karbidopa per dag moet verskaf word vir optimale onderdrukking van ekstraserebrale dekarboksilering van levodopa. Wanneer meer levodopa nodig is, moet LECARDOP 25/100 vervang word met LECARDOP 25/250. Indien nodig, kan die dosis LECARDOP 25/250 verhoog word met ‘n halwe of een tablet elke dag of elke tweede dag, tot ‘n maksimum van agt tablette ‘n dag. Ondervinding is beperk met totale daaglikse dosisse van meer as 200 mg karbidopa.

Maksimum aanbevole dosis:

Agt tablette LECARDOP 25/250 per dag (200 mg karbidopa en 2 g levodopa). Dit is ongeveer 3 mg/kg karbidopa en 30 mg/kg levodopa in ‘n pasiënt wat 70 kg weeg.

Pediatriese gebruik:

Veiligheid en doeltreffendheid vir pediatriese pasiënte is nie bepaal nie.

Die gebruik van LECARDOP vir pasiënte jonger as 18 jaar word nie aanbeveel nie.

4.3 Kontra-indikasies

- Bekende hipersensitiwiteit vir levodopa, karbidopa of enige bestanddeel van LECARDOP gelys in afdeling 6.1.

- Nou-hoek gloukoom.
- Ongediagnoseerde velletsel of ‘n geskiedenis van melanoom (aangesien dit bekend is dat levodopa ‘n kwaadaardige melanoom aktiveer).
- Swangerskap en borsvoeding (sien afdeling 4.6).
- Erge psigose.
- Nie-selektiewe monoamienoksidase (MAO) remmers is teenaangedui vir gebruik saam met LECARDOP. MAO-remmers moet vir ten minste 2 weke, voordat terapie met LECARDOP geïnisieer word, onttrek word. LECARDOP kan gelyktydig toegedien word volgens die vervaardiger se aanbevole dosis van ‘n MAO-remmer met selektiwiteit vir MAO-tipe B (bv. selegilien HCl) (sien afdeling 4.5).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

LECARDOP word nie aanbeveel vir die behandeling van medisyne-geïnduseerde ekstrapiramidale reaksies nie.

LECARDOP mag aan pasiënte wat alreeds levodopa alleen ontvang, gegee word alhoewel die levodopa alleen egter gestaak moet word ten minste 12 uur voordat met LECARDOP begin word. Plaasvervanging met LECARDOP moet gedoen word teen ‘n dosis wat ongeveer 20 % van die vorige levodopa dosis sal verskaf (sien afdeling 4.2).

Diskinesie mag voorkom in pasiënte wat voorheen met slegs levodopa behandel is, want karbidopa laat toe dat meer levodopa die brein bereik en meer dopamien dus gevorm word. Dit mag nodig wees om die dosis te verlaag indien diskinesie voorkom.

Monoamienoksidase (MAO) remmers moet gestaak word ten minste 2 weke voordat met terapie met LECARDOP begin word (sien afdeling 4.3).

LECARDOP moet versigtig toegedien word aan pasiënte met erge kardiovaskulêre of pulmonêre siekte, brongiale asma, nier-, lewer- of endokriene siekte, ‘n geskiedenis van peptiese ulkus (weens die moontlikheid van boonste gastro-intestinale bloeding) of konvulsies.

Versigtigheid word aangeraai wanneer LECARDOP aan pasiënte met ‘n geskiedenis van miokardiale infarksie toegedien word, wat residuele atriale, nodale, of ventrikulêre disritmieë het. Hartfunksie moet gemoniteer word, en besondere sorg moet geneem word by sulke pasiënte tydens die aanvanklike periode wat die dosis toegedien en getitreer word.

Periodieke evaluering van hepatiese, hematopoiëtiese, kardiovaskulêre en nierfunksie word gedurende terapie met LECARDOP aanbeveel. Die voorkoms van blefarospasma is ‘n teken van oordosering met LECARDOP.

‘n Simptoomkompleks wat ooreenkom met die neuroleptiese maligne sindroom, insluitende spierrigiditeit, verhoogde liggaamstemperatuur, geestesveranderings en verhoogde serumkreatien-fosfokinase is aangemeld wanneer anti-Parkinsonmedisyne skielik onttrek word.
Pasiënte moet daarom noukeurig dopgehou word wanneer die dosis van LECARDOP skielik verminder of gestaak word, veral as die pasiënt neuroleptiese middels ontvang.

Versigtigheid word aangeraai wanneer pasiënte met chroniese wye-hoek gloukoom behandel word. Pasiënte moet slegs behandeling met LECARDOP ontvang indien intraokulêre druk goed onder beheer is en die pasiënt tydens behandeling noukeurig gemoniteer word vir veranderings in intraokulêre druk.

Pasiënte met Parkinson se siekte het ‘n groter risiko om melanoom te ontwikkel. Dit is nie duidelik of die verhoogde risiko wat waargeneem word weens Parkinson se siekte is, of weens ander

faktore, soos medisyne wat gebruik word om Parkinson se siekte te behandel. Die vel moet periodiek deur toepaslik gekwalifiseerde deskundiges (bv. dermatoloë) ondersoek word, en pasiënte en hul versorgers word aangeraai om op te let vir melanome.

LECARDOP mag onwillekeurige bewegings en geestesversteurings veroorsaak. Daar word gereken dat hierdie reaksies weens verhoogde dopamienvlakke in die brein ná die toediening van levodopa is, en die gebruik van LECARDOP mag ‘n herhaling hiervan veroorsaak. Pasiënte met ‘n geskiedenis van erge onwillekeurige bewegings of psigotiese episodes moet noukeurig gemoniteer word. Dit mag nodig wees om die dosering te verlaag. Alle pasiënte moet noukeurig dopgehou word vir die ontwikkeling van depressie met begeleidende selfdoodneigings. Pasiënte met vorige of huidige psigoses moet versigtig hanteer word. Versigtigheid moet uitgeoefen word met gelyktydige toediening van psigo-aktiewe medisyne en LECARDOP (sien afdeling 4.5).

Pasiënte moet gereeld gemoniteer word vir die ontwikkeling van impulsbeheersteurings. Gedragsimptome van impulsbeheersteurings sluit in patologiese dobbel, verhoogde libido, hiperseksualiteit, kompulsiewe besteding of aankope, ooretery en kompulsiewe etery. Dit word aanbeveel dat die behandeling hersien word indien sulke simptome ontstaan.

Gelyktydige toediening van psigo-aktiewe medisyne, soos fenotiasiene of butirofenone, moet versigtig gedoen word en die pasiënt moet noukeurig dopgehou word vir ‘n verlies van die antiparkinsonistiese-effek (sien afdeling 4.5).

Pasiënte met ‘n geskiedenis van konvulsies moet met omsigtigheid behandel word.

Dopamiendisreguleringsindroom (DDS) is ‘n toegevoegde versteuring as gevolg van oormatige gebruik van die produk wat waargeneem word by sommige pasiënte wat met karbidopa/ levodopa

behandel word. Voordat met behandeling begin word, moet pasiënte en versorgers gewaarsku word van die potensiële risiko om DDS te ontwikkel (sien afdeling 4.8).

Laboratoriumtoetse:

Oor die algemeen is die vlakke van stikstof-bloeduream, kreatinien, en uriensuur laer tydens toediening van LECARDOP as met levodopa. Verbygaande abnormaliteite sluit verhoogde vlakke van bloedureum, AST (SGOT), ALT (SGPT), LDH, bilirubien, en alkaliese fosfotase in.

Verlaagde hemoglobien, hematokrit, verhoogde serumglukose en witbloedselle, bakterieë en bloed in die urine is aangemeld.

Positiewe Coombs se toetse is aangemeld, beide met LECARDOP en levodopa alleen.

LECARDOP mag ‘n vals positiewe uitslag veroorsaak wanneer ‘n toetsstrokie gebruik word om vir ketone in urine te toets; en hierdie reaksie word nie verander deur urine te kook nie. Die gebruik van glucose-oksidase metodes kan vals negatiewe resultate vir glikosurie oplewer.

4.5 Interaksie met ander medisyne en ander vorme van interaksie

Die volgende medisyne mag ‘n wisselwerking met LECARDOP hê:

Antihipertensiewe medisyne

Simptomatiese posturale hipotensie het voorgekom wanneer LECARDOP by die behandeling van ‘n pasiënt wat antihipertensiewe medisyne ontvang, gevoeg is. Wanneer terapie met LECARDOP begin word, mag dit dus nodig wees om die dosis van die antihipertensiewe medisyne aan te pas.

Antidepressante

Gelyktydige terapie met selegilien en karbidopa-levodopa kan geassosieer word met erge ortostatiese hipotensie, wat nie toegeskryf kan word aan die karbidopa-levodopa alleen nie (sien afdeling 4.3).

Ongunstige reaksies is aangemeld, insluitende hipertensie en diskinesie, weens die gelyktydige gebruik van trisikliese antidepressante en LECARDOP (sien afdeling 4.3 vir pasiënte wat MAO-remmers ontvang).

Ystersoute

Ystersoute mag die biobeskikbaarheid van levodopa en karbidopa verminder.

Ander medisyne:

- **Metoklopramied** mag die biobeskikbaarheid van levodopa laat toeneem deur maaglediging te verhoog. Metoklopramied mag ook siektebeheer nadelig beïnvloed weens die dopamienreseptor-antagonistiese eienskappe daarvan.
- **Anticholinergiese medisyne** (soos orfenadrien, triheksifenidiel, bensatropien en prosiklidien). Hoë bloeddruk of onwillekeurige liggaamsbewegings is aangemeld wanneer LECARDOP met ‘n trisikliese antidepressant gekombineer is.
- **Fenitoïen, papaverien, haloperidol en isoniasied** sal die effektiwiteit van LECARDOP verminder.
- **Dopamien D2 reseptoragoniste** (soos fenotiasiene, butirofenone en risperidoon) mag die terapeutiese effekte van levodopa verminder (sien afdeling 4.4).
- **‘n Hoëproteïendieet.** Levodopa, soos in LECARDOP, ding mee met sekere aminosure en ‘n hoëproteïendieet mag die absorpsie van levodopa belemmer.

- **Dopamien-uitputtingsmedisyne** (bv. reserpien en tetrabenasien). Gelyktydige gebruik met LECARDOP of ander medisyne wat daarvoor bekend is om mono-amienstore uit te put, word nie aanbeveel nie.

Die effek van gelyktydige toediening van teensuurmiddels saam met LECARDOP op die biobeskikbaarheid van levodopa is nie bestudeer nie.

LECARDOP kan aan pasiënte met Parkinson se siekte en sindroom wat vitamienpreparate wat piridoksien hidrochloried (vitamien B6) bevat, voorgeskryf word.

4.6 Swangerskap en laktasie

Swangerskap

Veiligheid en doeltreffendheid tydens swangerskap is nie bepaal nie. Kombinasies van karbidopa en levodopa het viserale en skeletale misvormings by hase veroorsaak (sien afdeling 4.3).

Laktasie

LECARDOP word in borsmelk uitgeskei.

Vrouens wat LECARDOP gebruik, moet nie hul suigelinge borsvoed nie (sien afdeling 4.3).

Vrugbaarheid

Geen data is beskikbaar nie.

4.7 Effekte op vermoë om te bestuut en masjinerie te gebruik

Skielike aanvang van slaap tydens daaglikse aktiwiteite, in sommige gevalle sonder waarskuwingstekens, slaperigheid en duiseligheid mag voorkom, wat die vermoë om ‘n voertuig te bestuur en masjinerie te hanteer kan belemmer. Versigtigheid word aangeraai voordat ‘n voertuig bestuur of masjinerie hanteer word, totdat die effekte van LECARDOP bekend is. Pasiënte wat

voorheen slaperigheid en/of ‘n episode van skielike slaapaanvang ervaar het, moet nie ‘n voertuig bestuur of masjinerie hanteer nie.

4.8 Ongewenste effekte

Newe-effekte wat dikwels voorkom by pasiënte wat LECARDOP ontvang, is dié as gevolg van die sentrale neurofarmakologiese aktiwiteit van dopamien.

Hierdie reaksies kan gewoonlik verminder word deur dosisverlaging. Die mees algemene newe-effekte is diskinesie, insluitende chorea-agtige, distoniese, en ander onwillekeurige bewegings en naarheid. Spiersametrekkings en blefarospasma kan as vroeë tekens gesien word om dosisvermindering te oorweeg.

Ander ernstige newe-effekte wat in kliniese proewe of in na-bemarkingservaring aangemeld is, sluit in:

Neoplasma benigne, maligne en ongespesifiseerd (insluitend siste en poliepe)

Minder dikwels: Maligne melanoom.

Bloed- en limfatiese stelselversteurings

Minder dikwels: Agranulositose, leukopenie, hemolitiese en nie-hemolitiese anemie en trombositopenie.

Immuunstelselversteurings

Minder dikwels: Angio-edeem.

Metabolisme versteurings

Dikwels: Anoreksie.

Minder dikwels: Gewigsverlies en gewigstoename.

Psigiatriese versteurings

Dikwels: Verwarring, depressie met of sonder selfdoodneigings, abnormale drome, hallusinasies en slapeloosheid.

Minder dikwels: Agitasie, angstigheid, disoriëntasie, tandeknes veral gedurende slaap, demensie, euforie, verhoogde libido, psigotiese episodes insluitende dwalings en paranoïede idees.

Voorkoms onbekend: Dopamiendisreguleringsindroom.

Senuweestelselversteurings

Dikwels: Diskinesie, bradikinetiese episodes (die “aan-af” verskynsel), duiseligheid, distonie, hoofpyn en parestesie.

Minder dikwels: Chorea, verminderde verstandelike skerpheid, ekstrapiramidale en beweginsversteurings, val, loopgangabnormaliteite, lomerigheid insluitend baie seldsame oormatige slaperigheid gedurende die dag en skielike aanvang van slaapepisodes, sinkopee, aktivering van latente Horner se sindroom, ataksie, konvulsies, floute, verhoogde bewing van die hande, gevoelloosheid, okulogiriese krisis, gevoel van stimulasie en kaakklem.

Oogversteurings

Minder dikwels: Diplopie, blefarospasma, wasige visie en verwyde pupille.

Kardiale versteurings

Minder dikwels: Palpitasie en kardiale onreëlmatighede.

Vasulêre versteurings

Dikwels: Ortostatiese effekte insluitende hipotensiewe episodes.

Minder dikwels: Blosing, warmgloede, hipertensie en flebitis.

Respiratoriese, torakale en mediastinale versteurings

Dikwels: Dispnee.

Minder dikwels: Bisarre asemhalingspatrone en heesheid.

Gastroïntestinale versteurings

Dikwels: Hardlywigheid, diarree, droë mond, dispepsie, naarheid en braking.

Minder dikwels: Gastroïntestinale pyn, bitter smaak, branderige sensasie van die tong, donker speeksel, ontwikkeling van duodenale ulkus, disfagie, winderigheid, gastroïntestinale bloeding, hik, en sialorree.

Vel- en subkutane weefselverteurings

Minder dikwels: Verhoogde sweet, urtikarie, alopesie, donker sweet, Henoch-Schönlein purpura, pruritus en uitslag.

Muskuloskeletale en bindweefselversteurings

Dikwels: Spierkrampe.

Minder dikwels: Spiersametrekkings.

Renale en urinêre versteurings

Minder dikwels: Donker urine, urinêre inkontinensie en urinêre retensie.

Voorplantingstelsel- en borsversteurings

Minder dikwels: Priapisme.

Algemene versteurings en toedienplektoestande

Minder dikwels: Astenie, malaise, edeem, vermoeidheid, neuroleptiese maligne sindroom (sien afdeling 4.4) en swakheid.

Ondersoeke

Minder dikwels: Abnormaliteite by verskeie laboratoriumtoetse het voorgekom met karbidopa-levodopa preparate en mag voorkom met LECARDOP. Hierdie sluit verhogings van lewerfunksietoetse soos alkaliese fosfatase, SGOT (AST), SGPT (ALT), melksuurdehidrogenase, bilirubien, stikstof-bloedureum, kreatinien, uriensuur en positiewe Coombs se toets in.

Verlaagde hemoglobien, hematokrit, verhoogde serumglukose en witbloedselle, bakterieë en bloed in urine is aangemeld.

Beskrywing van geselekteerde ongewenste reaksies

Dopamiendisreguleringsindroom (DDS):

DDS is ‘n toegevoegde versteuring wat by sommige pasiënte wat met karbidopa/levodopa behandel word. Geaffekteerde pasiënte toon ‘n kompulsiewe patroon van dopaminergiese medisyne misbruik bokant dosisse wat voldoende is om motoriese simptome te beheer, wat in sommige gevalle tot ernstige diskinesie mag lei (sien ook afdeling 4.4).

Impulsbeheerde versteurings:

Patologiese (kompulsiewe) dobbel, verhoogde libido, hiperseksualiteit, kompulsiewe besteding/aankope en ooretery/kompulsiewe eetpatroon kan voorkom by pasiënte wat met dopamienagoniste en/of ander dopaminergiese behandelings wat levodopa bevat, insluitende LECARDOP behandel is (sien afdeling 4.4).

Aanmelding van vermoedelike ongunstige reaksies

Aanmelding van vermoedelike ongunstige reaksies na goedkeuring van LECARDOP is belangrik. Dit verseker volgehoue monitering van die voordeel/risiko balans van LECARDOP. Gesondheidsorgvoorsieniers word versoek om enige vermoedelike ongunstige reaksies by SAHPRA aan te meld *via* die "**Adverse Drug Reactions Reporting Form**", wat aanlyn onder SAHPRA se publikasies beskikbaar is: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosis

Simptome

Sien afdeling 4.8.

Oordosering met LECARDOP kan blefarospasma en 'n onegalige hartspoed veroorsaak.

Behandeling

Aangesien daar geen teenmiddel vir 'n akute oordosis van LECARDOP is nie, is behandeling simptomaties en ondersteunend.

Piridoksien is nie effektief om die uitwerking van LECARDOP om te keer nie.

Algemene ondersteunende maatreëls moet ingestel word, saam met geaktiveerde houtskool. Intraveneuse vloeistowwe moet oordeelkundig toegedien word en 'n oop lugweg in stand gehou word. Elektrokardiografiese monitering moet ingestel word en die pasiënt moet noukeurig dopgehou word vir die ontwikkeling van disritmieë; indien nodig moet gepaste antidisritmiese terapie gegee word.

Die moontlikheid dat die pasiënt ander medisyne asook LECARDOP geneem het, moet in aanmerking geneem word. Tot op datum is daar geen ondervinding aangemeld met dialise nie; dus is die waarde by oordosering onbekend.

Die terminale half-leeftyd van levodopa is ongeveer twee uur in die teenwoordigheid van karbidopa.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Kategorie en klas: A 5.4.1 Anti-Parkinsonisme preparate

Farmakoterapeutiese groep: Levodopa: dopaminergiese middels; karbidopa: dopadekarboksilase-remmer.

ATC kode: N04BA02.

LECARDOP is ‘n onmiddellike vrystellingstablet wat ‘n kombinasie van karbidopa en levodopa bevat.

Levadopa is ‘n metaboliese voorganger van dopamien. Levodopa word vinnig gedekarboksileer na dopamien in weefsel buite die serebrum wanneer dit oraal toegedien word, sodat slegs ‘n klein gedeelte van ‘n toegediende dosis onveranderd vervoer word na die sentrale senuweestelsel. Karbidopa is ‘n inhibeerder van dopa-dekarboksilase wat in perifere weefsel voorkom. Toediening daarvan saam met levodopa voorkom perifere dekarboksilering van levodopa. Hierdie kombinasie verlaag dus die hoeveelheid levodopa wat nodig is met ongeveer 75 % en verhoog plasmavlakke en verleng die halfleeftyd van levodopa. Dit kruis nie die bloed-brein-skans nie en affekteer nie die metabolisme van levodopa in die sentrale senuweestelsel nie.

5.2 Farmakokinetiese eienskappe

Levodopa word vinnig maar veranderlik uit die gastro-intestinale weg geabsorbeer ná orale toediening in die afwesigheid van 'n dekarboksilase-inhibeerder. Die plasma-halfleeftyd van levodopa is ongeveer 1 uur. Tot soveel as 30 % van die levodopa word na 3-O-metieldopa omgeskakel, wat 'n halfleeftyd van 9 – 22 uur het. Ongeveer 80 % van die levodopa word binne 24 uur in die urine uitgeskei, hoofsaaklik as homovanilliensuur en dihidroksifenielasynsuur. Minder as 1 % van die dosis wat toegedien is, word onveranderd uitgeskei.

Karbidopa word vinnig, maar onvolledig, uit die gastro-intestinale weg geabsorbeer ná orale toediening in die afwesigheid van levodopa. Ongeveer 50 % van die toegediende dosis word in die urine uitgeskei, met ongeveer 3 % daarvan as die onveranderde moederverbinding, wat binne 7 uur verskyn.

Die eliminasiehalfleeftyd van levodopa in die teenwoordigheid van karbidopa is ongeveer 1,5 uur.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van onaktiewe bestanddele

Mieliestysel

Magnesiumstearaat

Mikrokristallyne sellulose

Voorafgelatiniseerde stysel

Natriumstyselglikolaat

D&C Geel nr. 10 aluminiumlak (LECARDOP 25/100)

FD&C Geel nr. 6 aluminiumlak (LECARDOP25/100)

FD&C Blou nr. 2 aluminiumlak (LECARDOP 25/250).

6.2 Onverenigbaarhede

Nie van toepassing nie.

6.3 Rakleeftyd

24 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring

Bewaar by of onder 25 °C.

Beskerm teen lig. Hou die bottel styf toe.

6.5 Aard en inhoud van houer

LECARDOP tablette word verpak in HDPE, wit, gladde, ronde bottels met ‘n wit geriffelde kinderbestande prop, met ‘n ontwerp aan die bokant. Die bottel word in ‘n gedrukte buitenste karton verpak.

Verpakking: 100 tablette.

6.6 Spesiale voorsorgmaatreëls vir vernietiging en ander hantering

Nie van toepassing nie.

7. HOUER VAN REGISTRASIESERTIFIKAAT

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8. REGISTRASIENOMMERS

LECARDOP 25/250: 45/5.4.1/0764

LECARDOP 25/100: 45/5.4.1/0765

9. DATUM VAN EERSTE GOEDKEURING/HERNUWING VAN DIE GOEDKEURING

25 November 2016

10. DATUM VAN HERSIENING VAN DIE TEKS

4 August 2022