1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CARBILEV 25/100 tablets

CARBILEV 25/250 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of CARBILEV 25/100 contains 25 mg carbidopa and 100 mg levodopa.

Sugar free

Each tablet of CARBILEV 25/250 contains 25 mg carbidopa and 250 mg levodopa.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CARBILEV 25/100 is a round, flat, yellow tablet with bevelled edges, bisected on one side and plain on the other side.

CARBILEV 25/250 is a light blue, round, biconvex tablet, bisected on one side and plain on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CARBILEV is indicated for:

- Treatment of Parkinson's disease and syndrome.
- To reduce "off" time in patients previously treated with levodopa/decarboxylase inhibitor preparations, or with levodopa alone, who have had motor fluctuations characterized by end-of-dose deterioration, peak dose dyskynesias, akinesia, or similar evidence of short-duration motor disturbances.

4.2. Posology and method of administration

Posology

Adults

General dosage information

Titrated dosage is necessary to achieve the individual therapeutic blood concentration requirements and to avoid side effects. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesia, chorea and dystonia. This is especially important for geriatric patients and those receiving other medicine.

The tablets should be taken with or after meals. When carbidopa/levodopa combination is to be discontinued, the dosage should be reduced gradually to prevent the occurrence of a syndrome that resembles the neuroleptic malignant syndrome.

Usual adult dosage

For patients not already treated with levodopa, dosage is best initiated with one tablet of CARBILEV 25/100, three times a day. Dosage may be increased by one tablet daily, or on alternate days, as necessary, to a maximum of eight tablets daily. For patients starting with

CARBILEV 25/250, the initial dose is half a tablet taken once or twice daily. An additional half a tablet may be added every day, or every other day, if necessary, until optimal response is reached. Carbidopa doses greater than 200 mg daily are not generally exceeded.

Maintenance dosage

One CARBILEV 25/250 tablet three times a day.

This dosage may be increased by half a tablet, or one tablet, every day, or every other day, to a maximum of eight tablets daily.

Patient conversion from levodopa

Levodopa must be discontinued for at least eight hours prior to conversion to CARBILEV therapy. As high central dopamine concentrations can be achieved quickly with carbidopa/levodopa, both beneficial and adverse effects tend to occur more rapidly than with levodopa alone, and patients should be monitored carefully during the dose adjustment period. A daily dosage of CARBILEV 25/100 or 25/250 should be chosen that will provide approximately 20 % to 25 % 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 CARBILEV 25/100 three to four times daily. The suggested starting dosage for most patients taking more than 1 500 mg levodopa daily is one tablet of CARBILEV 25/250 three to four times daily.

Special populations

Renal impairment

CARBILEV should be administered cautiously to patients with renal disease (see section 4.4).

Hepatic impairment

CARBILEV should be administered cautiously to patients with hepatic or endocrine disease (see section 4.4).

Cardiovascular disease

CARBILEV should be administered cautiously to patients with severe cardiovascular or pulmonary disease (see section 4.4).

Paediatric population

The safety of CARBILEV in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended (see section 4.4).

Method of administration

For oral administration.

4.3. Contraindications

CARBILEV is contraindicated in:

- Patients with hypersensitivity to carbidopa and levodopa or to any excipients in CARBILEV (see section 6.1).
- Monoamine oxidase (MAO) inhibitors and CARBILEV should not be given concurrently. It is recommended that MAO inhibitors be discontinued at least two weeks prior to initiating CARBILEV therapy.
- Patients with severe psychoses.
- Pregnancy and lactation. Carbidopa/levodopa combination has been associated with foetal abnormalities in animals and should therefore not be given to women of childbearing age.
- Since levodopa may activate a malignant melanoma, it should not be used in patients with

a history of malignant melanoma or skin disorders suggestive of it.

- Closed-angle glaucoma.
- Safety and efficacy in children under the age of 18 years has not been established (see section 4.2).

4.4. Special warnings and precautions for use

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

CARBILEV should be administered cautiously to patients with bronchial asthma, emphysema and other severe pulmonary and cardiovascular disease. Care should be exercised in administering CARBILEV to patients with a history of myocardial infarction, peptic ulcer, psychotic states, open-angle glaucoma, renal function impairment and urinary retention. These patients should be monitored with particular care during the period of initial dosage adjustment. Patients with diabetes mellitus should note that the use of CARBILEV may adversely affect control of glucose in the blood.

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. 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 (see section 4.7). 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, CARBILEV 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 CARBILEV is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa and use of CARBILEV 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 medicines. Therefore, any abrupt dosage reduction or withdrawal of CARBILEV should be carefully observed, particularly in patients who are also receiving neuroleptics.

Concomitant administration of psycho-active medicines 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 CARBILEV, provided the intra-ocular pressure is well controlled and the patient monitored carefully for

changes in intra-ocular pressure during therapy.

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

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the medicine 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).

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers 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 CARBILEV. Review of treatment is recommended if such symptoms develop.

Laboratory tests

Levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of CARBILEV than with levodopa. Transient abnormalities include elevated levels of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase (see section 4.8).

Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported (see section 4.8).

Positive Coombs' tests have been reported, both with CARBILEV and for levodopa alone. CARBILEV 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.

Paediatric population

CARBILEV is not recommended for children under the age of 18 years (see section 4.2).

4.5. Interaction with other medicines and other forms of interaction

Care should be exercised when administering CARBILEV with anaesthetics, anticonvulsants, haloperidol, phenothiazines, antihypertensives, monoamine oxidase (MAO) inhibitors (see section 4.3) and selegiline.

Antihypertensive medicines

Postural hypotension can occur when CARBILEV is added to the treatment of patients already receiving antihypertensive medicines. Dosage adjustment of the antihypertensive medicine may be required.

Antidepressants

Reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants (see section 4.3).

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.

Cocaine

Concurrent use with levodopa may increase the risk of cardiac dysrhythmias; if use of cocaine is necessary in patients receiving levodopa, it is recommended that cocaine be administered with caution, in reduced dosage and in conjunction with electrocardiographic monitoring.

Other medicines

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

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

Use of CARBILEV with dopamine-depleting medicines (e.g., tetrabenazine) or other medicines 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 section 4.3).

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

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

CARBILEV may be given to patients with Parkinson's disease and syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B_6).

4.6. Fertility, pregnancy and lactation

The safety of CARBILEV in pregnancy and lactation has not been established (see section 4.3).

Pregnancy

Although the effects of CARBILEV on human pregnancy are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits.

Breastfeeding

Levodopa is excreted in breast milk and may inhibit lactation.

It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue breastfeeding or discontinue the use of CARBILEV, taking into account the importance of the medicines to the mother.

Fertility

No data are available.

4.7. Effects on ability to drive and use machines

CARBILEV has a major influence on the ability to drive and use machines

Since adverse reactions such as dizziness and drowsiness have been reported in patients receiving CARBILEV, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that CARBILEV does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

Side effects that occur frequently with CARBILEV 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.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Neoplasm benign, malignant and unspecified (including cysts and polyps)			Malignant melanoma
Blood and the lymphatic system disorders		Haemolytic anaemia, transient leucopenia	Leucopenia, non-haemolytic anaemia, thrombocytopenia, agranulocytosis

Immune system disorders			Angioedema, urticaria, pruritus, Henoch-Schonlein purpura
Metabolism and nutrition disorders			Weight gain or loss, oedema.
Psychiatric disorders			Agitation, anxiety, euphoria, nightmares and insomnia, or sometimes drowsiness and depression, paranoid delusions, aggression hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, confusion, increased libido, somnolence, asthenia, decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle cramp, trismus, activation of latent Horner's syndrome, falling, gait abnormalities and Dopamine Dysregulation Syndrome, akinesia and rigidity.
Nervous system disorders	Dyskinesias including choreiform, dystonic and other involuntary movements,		Neuroleptic malignant syndrome which includes intermittent dystonia, alternating with substantial agitation, hyperthermia, and mental changes, bradykinetic episodes (the "on-off" phenomenon), dizziness, paraesthesia, headache
Eye disorders			Diplopia, blurred vision, dilated pupils, oculogyric crises.
Cardiac disorders			Cardiac irregularities and/or palpitations, orthostatic hypotension, effects including hypotensive episodes, hypertension, phlebitis.
Respiratory, thoracic and mediastinal disorders			Dyspnoea, bizarre breathing patterns
Gastrointestinal disorders	Nausea.		Vomiting, anorexia gastro-intestinal bleeding, development of duodenal ulcer, diarrhoea, dark saliva. dyspepsia, dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of the tongue
Skin and subcutaneous tissue disorders			Alopecia, rash, dark sweat, flushing, increased sweating.
Renal and urinary disorders			Dark urine. sweat or other body fluids, urinary retention, urinary incontinence, priapism
General disorders and administrative site conditions			Weakness, faintness, fatigue, hoarseness, malaise, hot flushes, sense of stimulation

c) Description of selected adverse reactions

Psychiatric disorders

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 section 4.4).

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 CARBILEV (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Muscle twitching and blepharospasm may be early signs of excessive dosage

Treatment

Management of acute overdosage with CARBILEV is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of CARBILEV. 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 medicines as well as CARBILEV 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

Category and Class: A 5.4.1 Anti-Parkinsonism Preparations

Pharmacotherapeutic group: Medicines affecting autonomic function

ATC code: N04BA02

Mechanism of action

CARBILEV 25/100 and CARBILEV 25/250 contains carbidopa, an aromatic amino acid decarboxylase inhibitor and levodopa, the metabolic precursor of dopamine, for the treatment of Parkinson's disease and syndrome.

Carbidopa, which does not cross the blood-brain barrier, inhibits the peripheral decarboxylation of levodopa, thus slowing its conversion to dopamine in extracerebral tissues. This results in an increased availability of levodopa for transport to the brain where it undergoes decarboxylation to dopamine, stimulating dopaminergic receptors in the basal ganglia. This improves the

balance between cholinergic and dopaminergic activity, resulting in improved modulation of voluntary nerve impulses transmitted to the motor cortex.

CARBILEV provides effective long-lasting levodopa plasma levels at doses that are approximately 80 % lower than those needed with levodopa alone.

While pyridoxine hydrochloride (Vitamin B_6) is known to accelerate the peripheral metabolism of levodopa to dopamine, carbidopa prevents this action.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

CARBILEV 25/100

Croscarmellose sodium, dye lennon lake yellow no. 520 (C.I No. 47005), magnesium stearate, microcrystalline cellulose, povidone K25, purified talc.

CARBILEV 25/250

Croscarmellose sodium, dye lennon blue no. 198, dye lennon lake blue no. 197, magnesium stearate, microcrystalline cellulose, povidone K25, purified talc.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C in an airtight container and protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

CARBILEV 25/100: 100 tablets are packed in white polypropylene securitainers with a package leaflet and a white rayon insert, and sealed with a white low density polyethylene snap-on cap, with a tamper-proof seal.

100 tablets are packed in a clear PVC film and aluminium foil blister packs, together with a package leaflet, into pre-printed cardboard unit cartons.

100 tablets are packed into amber round polypropylene, hingelid vials, together with a foam insert and package leaflet.

CARBILEV 25/250: 100 tablets are packed in white polypropylene securitainers with a package leaflet and white rayon insert, and sealed with a white low density polyethylene cap.

100 tablets are packed in a clear PVC film and aluminium foil blister packs, together with a package leaflet, into pre-printed cardboard unit cartons.

100 tablets are packed into amber round polypropylene, hingelid vials, together with a foam insert and package leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharmacare Limited

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

CARBILEV 25/100 - 30/5.4.1/0271

CARBILEV 25/250 - 30/5.4.1/0269

9. DATE OF FIRST AUTHORISATION

09 September 1996

10. DATE OF REVISION OF TEXT

24 December 2020

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