SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SINEMET® 25/100 Tablets

SINEMET® 25/250 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SINEMET 25/100 Tablet contains carbidopa monohydrate equivalent to 25 mg anhydrous carbidopa and 100 mg levodopa.

Each SINEMET 25/250 Tablet contains carbidopa monohydrate equivalent to 25 mg anhydrous carbidopa and 250 mg levodopa.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SINEMET 25/100 Tablet is a yellow, oval-shaped tablet, plain on one side, debossed with 650 on the other side.

SINEMET 25/250 Tablet is a light dapple blue, oval-shaped tablet, plain on one side, scored and debossed with 654 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SINEMET is indicated for the treatment of Parkinson's disease and syndrome. It is useful in relieving many of the symptoms of Parkinsonism, particularly rigidity and bradykinesia.

SINEMET 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

Posology

General considerations

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

Studies show that the peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg daily. Patients receiving optimal carbidopa together with L-dopa experience less nausea and vomiting.

Standard anti-Parkinson drugs, other than levodopa alone, may be continued while SINEMET is being administered, although their dosage may have to be adjusted.

If general anaesthesia is required, SINEMET 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.

How to transfer patients from Levodopa

Because both therapeutic and adverse responses occur more rapidly with SINEMET than when levodopa is given alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with SINEMET 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 SINEMET is started (24 hours for slow-release preparations of levodopa). A daily dosage of SINEMET should be chosen that will provide approximately 20 % of the previous levodopa daily dosage.

Method of administration

Usual initial dosage

Dosage is best initiated with one tablet of SINEMET 25/100 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by 1 tablet every day or every other day, as necessary, until a dosage equivalent of 8 tablets of SINEMET 25/100 a day is reached.

For patients starting with SINEMET 25/250, the initial dose is ½ tablet taken once or twice daily. However, this may not provide the optimal amount of carbidopa needed by many patients. If necessary, add ½ 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 7 days as compared to weeks or months with levodopa alone.

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

Maintenance

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, SINEMET 25/250 should be substituted for SINEMET 25/100. If necessary, the dosage of SINEMET 25/250 may be increased by ½ or 1 tablet every day or every other day to a maximum of 8 tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Maximum recommended dose

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

Special populations

Use in the elderly

There is wide experience in the use of this product in elderly patients. The recommendations set out above reflect the clinical data derived from this experience.

Use in children

The safety of SINEMET 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).

4.3 Contraindications

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with SINEMET. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET. SINEMET 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). Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

SINEMET is contraindicated in patients with narrow angle glaucoma.

Since levodopa may activate a malignant melanoma, SINEMET should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.
See also section 4.6.

4.4 Special warnings and precautions for use

SINEMET is not recommended for the treatment of drug-induced extrapyramidal reactions.

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

The occurrence of dyskinesias may require dosage reduction.

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

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

Care should be exercised in administering SINEMET to patients with a history of myocardial infarction who have residual atrial, nodal or ventricular arrhythmia. In such patients, cardiac function should be monitored with particular care during the period of initial dosage administration and titration.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET, provided the intraocular pressure is well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

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 agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

As with levodopa, periodic evaluations of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using SINEMET for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).

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 (such as pathological gambling, hypersexuality, increased libido, compulsive spending/buying and binge/compulsive eating) have been reported in patients treated with dopamine agonists and/or other dopaminergic treatment for Parkinson's disease. Review of treatment is recommended if such symptoms develop.

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/ levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

Usage in children

The safety and effectiveness of SINEMET in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

4.5 Interaction with other medicines and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with SINEMET:

Antihypertensive agents: Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required.

Antidepressants: For patients receiving monoamine oxidase inhibitors (see section 4.3). There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Iron: Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate.

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

Use of SINEMET with dopamine-depleting agents (e.g. reserpine and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Although the effects of SINEMET on human pregnancy are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Therefore, use of SINEMET in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Breastfeeding

It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. Because many 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 nursing or to discontinue the use of SINEMET, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

Levodopa has been associated with somnolence and episodes of sleep onset. Sudden onset of sleep during daily activities in some cases without awareness or warning signs has been reported very rarely. Patients should 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.

4.8 Undesirable effects

Side effects that occur frequently in patients receiving SINEMET 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:

Very Common (> 1/10)

Infections and infestations: urinary tract infections

Nervous system disorders: dyskinesias.

Common (> 1/100, < 1/10)

Metabolism and nutrition disorders: anorexia

Psychiatric disorders: confusion, depression with or without suicidal tendencies, dream abnormalities, hallucinations and insomnia

Nervous system disorders: bradykinetic episodes (the “on-off” phenomenon), dizziness, dystonia, headache and paraesthesia

Vascular disorders: orthostatic effects including hypotensive episodes

Respiratory disorders: dyspnoea

Gastrointestinal disorders: constipation, diarrhoea, dry mouth, dyspepsia, nausea and vomiting

Musculoskeletal, connective tissue and bone disorders: muscle cramps

General disorders: chest pain.

Uncommon (> 1/1 000, < 1/100)

Metabolism and nutrition disorders: weight loss

Psychiatric disorders: agitation, anxiety and disorientation

Nervous system disorders: chorea, decreased mental acuity, extrapyramidal and movement disorders, falling, gait abnormalities, somnolence including very rarely excessive daytime somnolence and sudden sleep onset episodes and syncope

Eye disorders: diplopia

Cardiac disorders: palpitation

Gastrointestinal disorders: gastrointestinal pain

Skin and subcutaneous disorders: increased sweating and urticaria

General disorders: asthenia and malaise.

Rare (> 1/10 000, < 1/1 000)

Immune system disorders: angioedema

Neoplasms benign and malignant: malignant melanoma (see section 4.3)

Blood and the lymphatic system disorders: agranulocytosis, leukopenia, haemolytic and non-haemolytic anaemia and thrombocytopenia

Metabolism and nutrition disorders: weight gain

Psychiatric disorders: bruxism, dementia, euphoria, increased libido, psychotic episodes including delusions and paranoid ideation

Nervous system disorders: activation of latent Horner's syndrome, ataxia, convulsions, faintness, increased hand tremor, numbness, oculogyric crises, sense of stimulation and trismus.

In post-marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying and binge/compulsive eating has been reported rarely in patients treated with dopamine agonists and/or other dopaminergic treatments and rarely in patients treated with levodopa, including SINEMET (see section 4.4).

Eye disorders: blepharospasm, blurred vision and dilated pupils

Cardiac disorders: cardiac irregularities

Vascular disorders: flushing, hot flashes, hypertension and phlebitis

Respiratory disorders: bizarre breathing patterns and hoarseness

Gastrointestinal disorders: bitter taste, burning sensation of tongue, dark saliva, development of duodenal ulcer, dysphagia, flatulence, gastrointestinal bleeding, hiccups and sialorrhoea

Skin and subcutaneous disorders: alopecia, dark sweat, Henoch-Schönlein purpura, pruritus and rash

Musculoskeletal, connective tissue and bone disorders: muscle twitching

Renal and urinary disorders: dark urine, urinary incontinence and urinary retention

Reproductive system disorders: priapism

General disorders: oedema, fatigue, neuroleptic malignant syndrome (see section 4.4) and weakness

Unknown

Nervous System/Psychiatric: Dopamine Dysregulation Syndrome

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

Investigations:

Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with SINEMET. 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.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glycosuria.

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. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Health care providers can also report any side effects directly to Organon's Pharmacovigilance Unit at dpoc.zaf@organon.com or Tel: +27 (0) 10 344 0706.

4.9 Overdose

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

Electrocardiographic monitoring should be instituted and the patient carefully observed for the possible development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET should be taken into consideration. To date, no experience has been reported with dialysis; hence its value in overdosage is not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.5.4.1 Anti-Parkinsonism Preparations

SINEMET is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor and levodopa, the metabolic precursor of dopamine, for the treatment of Parkinson's disease and syndrome.

Levodopa relieves the symptoms of Parkinson's disease by being decarboxylated to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extra-cerebral decarboxylation of levodopa, making more levodopa available for transport to

the brain and subsequent conversion to dopamine. SINEMET 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.

5.2 Pharmacokinetic properties

Absorption

Levodopa

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastro-intestinal tract. It has a plasma half-life of about 1 hour and is mainly converted by decarboxylation to dopamine, a proportion of which is converted to noradrenaline. Up to 30 % is converted to 3-O-methyldopa which has a half-life of 9 to 22 hours. About 80 % of levodopa is excreted in the urine within 24 hours mainly as homovanillic acid and dihydroxyphenylactic acid. Less than 1% is excreted unchanged.

Once in the circulation it competes with other neutral amino acids for transport across the blood brain barrier. Once it has entered the striatal neurones it is decarboxylated to dopamine, stored and released from presynaptic neurones. Because levodopa is so rapidly decarboxylated in the gastro-intestinal tract and the liver, very little unchanged compound is available for transport into the brain. The peripheral decarboxylation reduces the therapeutic effectiveness of levodopa but is responsible for many of its side effects. For this reason levodopa is usually administered together with a peripheral decarboxylase inhibitor such as carbidopa, so that lower doses may be given to achieve the same therapeutic effect.

Carbidopa

Carbidopa in the absence of levodopa, is rapidly but incompletely absorbed from the gastrointestinal tract following oral dosing. Following an oral dose approximately 50% is recorded in the urine, with about 3% of this as unchanged compound. It does not cross the blood brain barrier but crosses the placenta and is excreted in breast milk.
Turnover of the compound is rapid and virtually all unchanged compound appears in the urine within 7 hours.

Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine but as it does not cross the blood brain barrier, effective brain levels of dopamine get produced with lower levels of levodopa therapy reducing the peripheral side effects, noticeably nausea and vomiting and cardiac dysrhythmias.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Corn starch, magnesium stearate, microcrystalline cellulose, pregelatinised starch, Yellow D & C No. 10 (Quinoline Yellow E-104), FD & C Blue No. 2 (Indigotine) and purified water.

Yellow D & C No. 10 (Quinoline Yellow E-104) is only found in SINEMET 25/100 and FD & C Blue No. 2 (Indigotine) is only found in SINEMET 25/250.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Sinemet 25/ 100 mg and Sinemet 25/ 250 mg: 24 months

6.4 Special precautions for storage

Keep in the original container and keep the container tightly closed. Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

SINEMET 25/100 Tablets are supplied in bottles of 100.

SINEMET 25/250 Tablets are supplied in bottles of 100.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor

22 Magwa Crescent, Gateway West

Waterfall City, Midrand

2090

South Africa

Tel. No.: +27 (0) 10 344 0706

8. REGISTRATION NUMBERS

SINEMET 25/100: P/5.4.1/141

SINEMET 25/250: F/5.4.1/56

9. DATE OF FIRST AUTHORISATION

Date of registration:

SINEMET 25/100: 05 August 1982

SINEMET 25/250: 05 September 1973

10. DATE OF REVISION OF THE TEXT

Date of the most recent revision: 31 March 2026

Namibia Only: Sinemet 25/100

Registration Number-13/5.4.1/0005

Scheduling Status-NS2

Namibia Only: Sinemet 25/250

Registration Number-13/5.4.1/0006

Scheduling Status-NS2

Botswana Only: Sinemet 25/100

Registration Number-B9316005

Scheduling Status-S2

Botswana Only: Sinemet 25/250

Registration Number-B9316000

Scheduling Status-S2

RCN100003041