## SCHEDULING STATUS

S4

## PROPRIETARY NAME AND DOSAGE FORM

SINEMET® 25/100 Tablets

SINEMET® 25/250 Tablets

## 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.

**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.

Sugar free.

## PHARMACOLOGICAL CLASSIFICATION

A.5.4.1 Anti-Parkinsonism Preparations

## PHARMACOLOGICAL ACTION

SINEMET is a combination of carbidopa MSD, an aromatic amino acid decarboxylase inhibitor and levodopa MSD, 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.

**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.

**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 **“INTERACTIONS, Other medicines”**).

SINEMET is contraindicated in patients with known hypersensitivity to any component of this medication and 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.

**WARNINGS AND SPECIAL PRECAUTIONS**

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 **"DOSAGE AND DIRECTIONS FOR USE"**).

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 **"INTERACTIONS"**).

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.

**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.

**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.

**INTERACTIONS**

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 **"CONTRAINDICATIONS"**). 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 agonists (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 **"CONTRAINDICATIONS"**).

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

## 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.

**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 nursing or to discontinue the use of SINEMET, taking into account the importance of the medicine to the mother.

## DOSAGE AND DIRECTIONS FOR USE

**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.

**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.

**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.

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.

**SIDE 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)**

**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 **"CONTRAINDICATIONS"**)

**Blood and the lymphatic system disorders:** Agranulocytosis, leucopenia, 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 **"WARNINGS AND SPECIAL PRECAUTIONS"**).

**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-Schoenlein 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 **"WARNINGS AND SPECIAL PRECAUTIONS"**) and weakness

**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.

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

## IDENTIFICATION

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.

**PRESENTATION**

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

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

**STORAGE INSTRUCTIONS**

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

Protect from light.

Keep out of reach of children.

**REGISTRATION NUMBERS**

SINEMET 25/100: P/5.4.1/141

SINEMET 25/250: F/5.4.1/56

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

Organon South Africa (Pty) Ltd

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**DATE OF PUBLICATION OF THE PACKAGE INSERT**

15 September 2006 (Revision 1: 18 June 2015)

| 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 |

IPC-M0295B-T 082013