SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SINEMET® CR Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SINEMET CR Tablet contains carbidopa monohydrate equivalent to 50 mg anhydrous carbidopa and 200 mg levodopa.

Sugar free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SINEMET CR Tablet is a peach, oval-shaped tablet, deep score on one side, 521 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 characterised by end-of-dose deterioration ("wearing-off" phenomenon), peak dose dyskinesias, akinesia or similar evidence of short-duration motor disturbances.

4.2 Posology and method of administration

Posology

General considerations

SINEMET CR tablets contain a 1:4 ratio of carbidopa to levodopa.

The daily dosage of SINEMET CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

SINEMET CR may be administered as whole or as half tablets. So that the controlled release properties of the product can be maintained, tablets should not be chewed or crushed.

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

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine hydrochloride (vitamin B_6). It must be taken into account that the bioavailability of SINEMET CR is increased in the presence of food.

Method of administration

Initial dosage

Patients who have not received prior Levodopa therapy

The initial recommended dose is 1 tablet of SINEMET CR two or three times daily. Initial dosages should not exceed 600 mg per day of levodopa or be given at intervals of less than 6 hours.

Patients currently treated with conventional Levodopa/Decarboxylase inhibitor combinations

Dosage with SINEMET CR should be substituted at an amount that provides approximately 10 to 30 % more levodopa per day depending on the clinical response (see **Titration** below). The interval between doses should be 4 to 8 hours during the waking day.

A guide for substitution of SINEMET CR treatment is shown in the table below:

Guidelines for Initial Conversion

From Levodopa/decarboxylase inhibitor to SINEMET CR

LEVODOPA/DECARBOXYLASE INHIBITOR	SINEMET CR
Total Daily Dose* Levodopa (mg)	Suggested Dosage Regimen
300 to 400	1 tablet two times daily.
500 to 600	1½ tablet two times daily or 1 tablet three times daily.
700 to 800	A total of 4 tablets in 3 or more divided doses (e.g. 1½ tablets a.m., 1½ tablets early p.m. and 1 tablet later p.m.).
900 to 1 000	A total of 5 tablets in 3 or more divided doses (e.g. 2 tablets a.m., 2 tablets early p.m. and 1 tablet later p.m.)

*For dosing ranges not shown in table see section 4.2 Posology and method of administration, **Initial dosage, Patients currently treated with conventional Levodopa/decarboxylase inhibitor combinations"**.

Patients currently treated with Levodopa alone

Levodopa must be discontinued at least 8 hours before therapy with SINEMET CR is started. In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR two or three times daily.

Titration

Following initiation of therapy, doses and dosing intervals may be increased or decreased, depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets of SINEMET CR per day, administered as divided doses at intervals ranging from 4 to 12 hours during the waking day. Higher doses (up to 12 tablets) and shorter intervals (< 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day. In some patients the onset

of effect of the first morning dose may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of SINEMET CR may be required.

Addition of other anti-Parkinson medications

Anticholinergic agents, dopamine agonists and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added to an existing treatment regimen for SINEMET CR.

A dose of SINEMET 25/100 (one half of a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

Interruption of therapy

Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics (see section 4.4).

If general anaesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

Special populations

Use in Children

Safety and effectiveness of SINEMET CR in infants and children have 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 CR. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET CR. SINEMET CR 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 CR is contraindicated in patients with narrow angle glaucoma.

Since levodopa may activate a malignant melanoma, SINEMET CR 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 CR 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.

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least 8 hours before therapy with SINEMET CR is started (at least 12 hours if slow-release plain levodopa has been administered).

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.

SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. 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.

SINEMET CR 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 or of convulsions.

Care should be exercised in administering SINEMET CR to patients with a history of recent 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 CR, 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 or discontinued, especially if the patient is receiving neuroleptics.
SINEMET CR is not recommended for the treatment of drug-induced extrapyramidal reactions.

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 CR 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).

Use in children

Safety and effectiveness of SINEMET CR 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 medicines are administered concomitantly with SINEMET CR:

Antihypertensive agents

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

Antidepressants

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

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. 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 CR should be observed carefully for loss of therapeutic response.

Use of SINEMET CR 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).

4.6 Fertility, pregnancy, and lactation

Pregnancy

Although the effects of SINEMET CR 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 CR 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 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 CR, 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

The side effect reported most frequently was dyskinesia (a form of abnormal involuntary movement). A somewhat greater incidence of dyskinesias was seen with SINEMET CR than with SINEMET due to the replacement of “off” time (which is reduced with SINEMET CR) by “on” time (which is sometimes accompanied by dyskinesias).

Side effects that were reported frequently were: nausea, hallucinations, confusion, dizziness, chorea and dry mouth.

Side effects occurring less frequently were: dream abnormalities, dystonia, somnolence, insomnia, depression, asthenia, vomiting and anorexia.

Other 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, 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 CR (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-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 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.

Investigations:

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

General supportive measures should be employed. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the possible development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consideration. To date, no experience has been reported with dialysis, hence its value in overdosage is not known.

Pyridoxine hydrochloride (vitamin B_6) has no effect in reversing the actions of SINEMET CR.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.5.4.1 Anti-Parkinsonism Preparations

SINEMET CR is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor and levodopa, the metabolic precursor of dopamine.

SINEMET CR contains carbidopa, 50 mg and levodopa, 200 mg per tablet, in a controlled-release formulation designed to release the active ingredients over a 4 to 6 hour period. With this formulation there is less variation in plasma levodopa levels and the peak plasma level is 60 % lower than with conventional SINEMET.

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.

5.2 Pharmacokinetic properties

Absorption

Levodopa

The pharmacokinetics of levodopa following administration of SINEMET CR were studied in young and elderly healthy volunteers.

The mean time to peak plasma levodopa level after SINEMET CR was approximately two hours compared to 0,75 hours with SINEMET.

The mean peak plasma levodopa levels were 60 % lower with SINEMET CR than with SINEMET.

The in vivo absorption of levodopa following administration of SINEMET CR was continuous for 4 to 6 hours.

In these studies, as with patients, plasma levodopa concentrations fluctuated in a narrower range than with SINEMET.

Because the bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70 %, the daily dosage of levodopa in the controlled release formulation will usually be higher than with conventional formulations.

There was no evidence that SINEMET CR released its ingredients in a rapid or uncontrolled fashion.

It is not known whether or not or to what extent the absorption is influenced by a protein rich diet. The bioavailability may be influenced by compounds which affect the gastro-intestinal propulsion.

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: hydroxypropyl cellulose, magnesium stearate, polyvinyl acetate crotonic acid co-polymer, red ferric oxide, quinoline yellow aluminium lake.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of the container

SINEMET CR Tablets are supplied in bottles of 100.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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