Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sinemet 12.5 mg/50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Sinemet 12.5mg/50mg contains carbidopa (equivalent to 12.5 mg of anhydrous carbidopa) and 50 mg levodopa.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Sinemet 12.5 mg/50 mg: yellow, oval-shaped tablets, with '520' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Antiparkinsonian agent.

For treatment of Parkinson's disease and syndrome. Sinemet is useful in relieving many of the symptoms of parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability associated with Parkinson's disease and syndrome.

When response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not controlled evenly throughout the day, substitution of Sinemet usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, Sinemet permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

Sinemet may be given to patients with Parkinson's disease and syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

4.2 Posology and method of administration

To be taken orally.

The optimum daily dosage of Sinemet must be determined by careful titration in each patient.

Sinemet Tablets are available as:-

Sinemet 12.5mg/50mg containing carbidopa Ph. Eur. equivalent to 12.5 mg of anhydrous carbidopa and 50 mg levodopa.

Sinemet 10mg/100mg containing carbidopa Ph. Eur. equivalent to 10 mg of anhydrous carbidopa and 100 mg levodopa. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. If subdivided, the tablet should be consumed as a whole dose.

Sinemet Plus containing carbidopa Ph. Eur. equivalent to 25 mg of anhydrous carbidopa and 100 mg levodopa..

Sinemet 25mg/250mg containing carbidopa Ph. Eur. equivalent to 25 mg of anhydrous carbidopa and 250 mg levodopa. The tablet can be divided into equal doses.

Advise the patient not to apply too much force when removing the tablet from the blister packaging. If the tablet breaks when it is removed from the blister packaging, it should be consumed only if the whole dose can be taken. If it cannot, the pieces of the broken tablet should be discarded, and another tablet taken from the packaging.

Administration of a partial dose may result in worsening of symptoms.

General Considerations
Dosage should be titrated to 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 a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. The formulations of Sinemet are designed to provide a range of doses with sufficient carbidopa to inhibit peripheral dopa-decarboxylase and thus exert optimal therapy.

Standard antiparkinsonian drugs, other than levodopa alone, may be continued while Sinemet is being administered, although their dosage may have to be adjusted.

Usual initial dosage
Dosage is best initiated with one tablet of Sinemet Plus 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 a dosage equivalent of eight tablets of Sinemet Plus a day is reached.

Sinemet 12.5 mg/50 mg or Sinemet 10 mg/100 mg may be used to facilitate dosage titration according to the needs of the individual patient.

If Sinemet 10mg/100mg or Sinemet 12.5mg/50mg is used, dosage may be initiated with one tablet three or four times a day. However, this may not provide the optimal amount of carbidopa needed by many patients. Titration upward may be required in some patients to achieve optimum dosage of carbidopa. The dosage may be increased by one tablet every day or every other day until a total of eight tablets (two tablets four times a day) 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 'Sinemet' than when levodopa is given, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with 'Sinemet' than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Discontinue levodopa at least 12 hours (24 hours for slow-release preparations of levodopa) before starting therapy with Sinemet. 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 of levodopa a day should be started on one tablet of Sinemet Plus three or four times a day. The suggested starting dosage for most patients taking more than 1,500 mg of levodopa is one tablet of Sinemet 25mg/250mg three or four times a day.

Maintenance
Therapy with Sinemet should be individualised and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided for optimal inhibition of extracerebral decarboxylation of levodopa. When a greater proportion of carbidopa is required, one tablet of Sinemet Plus 25 mg/100 mg or Sinemet 12.5 mg/50 mg may be substituted for each tablet of Sinemet 10 mg/100 mg.

Sinemet Plus may be helpful, especially for patients with nausea and vomiting.

When more levodopa is required, Sinemet 25mg/250mg should be substituted for Sinemet Plus 25 mg/100 mg or Sinemet 10 mg/100 mg, or Sinemet 12.5 mg/50 mg. If necessary, the dosage of Sinemet 25mg/250mg may be increased by 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 carbidopa is limited.

Maximum recommended dose

Eight tablets of Sinemet 25 mg/250 mg 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.

Patients receiving levodopa with another decarboxylase inhibitor
When transferring a patient to Sinemet from levodopa combined with another decarboxylase inhibitor, its dosage should be discontinued at least 12 hours before Sinemet is started. Begin with a dosage of Sinemet that will provide the same amount of levodopa as contained in the other levodopa/decarboxylase inhibitor combination.

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.

Use in the elderly
In the elderly, dosage should generally be low with slow and minimal increments.

4.3 Contraindications

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Sinemet. These inhibitors must be discontinued at least two weeks before starting therapy with Sinemet. Sinemet may be administered concomitantly with the manufacturer's lowest recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline hydrochloride). (See 4.5 'Interactions with other medicinal products and other forms of interaction').

Sinemet is contraindicated in patients with narrow-angle glaucoma and in patients with known hypersensitivity to any component of this medication.

Since levodopa may activate a malignant melanoma, Sinemet should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

Use in patients with severe psychoses.

4.4 Special warnings and precautions for use

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

Sinemet should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastro-intestinal haemorrhage).

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 very rarely. 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. 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 concomitant suicidal tendencies, and other serious antisocial behaviour. Patients with past or 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.

Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone should be observed carefully when Sinemet is substituted.
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.

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

If concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones is necessary, such drugs should be administered 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 Sinemet, provided the intra-ocular pressure is well controlled and the patient monitored carefully for changes in intra-ocular pressure during therapy.

Care should be exercised when Sinemet is administered to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.

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).

If general anaesthesia is required, therapy with Sinemet may be continued for 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.

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).

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

Laboratory Tests
Transient abnormalities in laboratory test results may occur, but have not been associated with clinical evidence of disease. These include elevations of blood urea nitrogen, AST (SGOT), ALT (SGPT), LDH, bilirubin, creatinine, uric acid, and alkaline phosphatase.

Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Sinemet than with levodopa.

Decreased haemoglobin and 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 Sinemet and levodopa alone, but haemolytic anaemia is extremely rare.

Sinemet may cause a false positive result for ketonuria when a dipstick is used to test for urinary ketone bodies; and this reaction is not altered by boiling the urine specimen. The use of glucose oxidase methods may give false negative results for glycosuria.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with Sinemet.

Antihypertensive agents

Symptomatic postural hypotension has occurred when Sinemet is added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with Sinemet is started, dosage adjustment of the antihypertensive drug may be required.

Antidepressants
Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants. (For patients receiving monoamine oxidase inhibitors, see 4.3 'Contraindications').

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

Other drugs
Dopamine D_2 receptor antagonists (eg. phenothiazines, butyrophenones and risperidone, thioxanthenes) and isoniazid may reduce the therapeutic effect of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs 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 4.3 'Contraindications').

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of carbidopa/levodopa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Carbidopa/levodopa is not recommended during pregnancy or in women of childbearing potential not using contraception unless the benefits for the mother outweigh the possible risk to the foetus.

Breast-feeding
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 drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue breast-feeding or discontinue the use of Sinemet, taking into account the importance of the drug to the mother.

Fertility
In reproduction studies with Sinemet, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily dose of levodopa.

4.7 Effects on ability to drive and use machines

No data are known about the effect on the ability to drive. If side effects such as dizziness or somnolence occur, they may affect the ability to drive and to operate machinery.

Patients being treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also 4.4 'Special warnings and precautions for use').

4.8 Undesirable effects

In controlled clinical trials in patients with moderate to severe motor fluctuations Sinemet CR or Half Sinemet CR did not produce side-effects which were unique to the controlled-release formulation.

The side-effect reported most frequently was dyskinesia (a form of abnormal involuntary movements). A greater incidence of dyskinesias was seen with Sinemet CR than with Sinemet.

Other side-effects that also were reported frequently (above 2%) were: nausea, hallucinations, confusion, dizziness, chorea and dry mouth.

Side effects occurring less frequently (1-2%) were: dream abnormalities, dystonia, insomnia, depression, asthenia, vomiting and anorexia.

Other side effects reported in clinical trials or in post-marketing experience include:

Body as a whole: chest pain, muscle cramps, syncope.

Cardiovascular: palpitation, orthostatic effects including hypotensive episodes.

Gastrointestinal: constipation, diarrhoea, dyspepsia, gastrointestinal pain, dark saliva.

Hypersensitivity: angioedema, urticaria, pruritus.

Metabolic: weight loss.

Nervous System/Psychiatric: Neuroleptic malignant syndrome, (See section 4.4 'Special warnings and precautions for use'), agitation, anxiety, decreased mental acuity, paraesthesia, disorientation, fatigue, headache, extrapyramidal and movement disorders, falling, gait abnormalities, on-off phenomenon, increased libido, psychotic episodes including delusions, hallucinations and paranoid ideation. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Respiratory: dyspnoea

Skin: flushing, alopecia, skin rash, dark sweat.

Special senses: blurred vision.

Urogenital: dark urine.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side-effects with Sinemet CR are listed below.

Infections and infestations: Urinary tract infections (very common)

Cardiovascular: Cardiac irregularities, hypertension, phlebitis.

Gastrointestinal: Bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

Haematologic: Leukopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

Nervous system/psychiatric: Ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome. Euphoria, dementia, and depression with or without suicidal tendencies, 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).

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 Sinemet CR or Half Sinemet CR (see section 4.4 'Special warnings and precautions for use').

Skin: Increased sweating.

Special senses: Diplopia, dilated pupils, oculogyric crises.

Urogenital: Urinary retention, urinary incontinence, priapism.

Miscellaneous: Weight gain, oedema, weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see 4.3 'Contraindications'). Henoch-Schönlein purpura. Convulsions have occurred; however, a causal relationship with levodopa or levodopa/carbidopa combinations has not been established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

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. 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 drugs as well as Sinemet 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopa and dopa derivatives, ATC code: N04BA02.

Levodopa is a precursor of dopamine, and is given as replacement therapy in Parkinson's disease.

Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of levodopa can be used, reducing the incidence and severity of side effects.

5.2 Pharmacokinetic properties

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastrointestinal 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 gastrointestinal tract and the liver very little unchanged drug 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 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 30 % of this as unchanged drug. It does not cross the blood brain

barrier but crosses the placenta and it is not known whether carbidopa is excreted in human milk. Turnover of the drug is rapid and virtually all unchanged drug 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 arrhythmias.

5.3 Preclinical safety data

Sinemet is well established in medical use. Preclinical data is broadly consistent with clinical experience.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sinemet 12.5mg/50mg tablets contain quinoline yellow (E104), maize starch, pregelatinised maize starch, microcrystalline cellulose, magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Sinemet 12.5mg/50mg:
Bottles: 2 years.

6.4 Special precautions for storage

Sinemet 12.5mg/50mg:
Bottles:
Do not store above 25°C. Keep the bottle tightly closed. Store in the original package.

6.5 Nature and contents of container

Sinemet 12.5mg/50mg:
HDPE bottle of 84, and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Organon Pharma (Ireland) Limited
2 Dublin Landings
North Wall Quay - North Dock
Dublin
D01 V4A3
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 February 1990

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

October 2023