Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sinemet CR 50mg/200mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains carbidopa (equivalent to 50mg of anhydrous carbidopa) and 200mg levodopa.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Product imported from Italy:
Peach-coloured, oval-shaped biconvex tablets, scored and marked ‘521’ on one side and plain on the other’

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Antiparkinson agent

Idiopathic Parkinson's disease, in particular to reduce off-period in patients who previously have been treated with levodopa/decarboxylase inhibitors, or with levodopa alone and who have experienced motor fluctuations. The experience is limited with ‘Sinemet’ CR and Half ‘Sinemet’ CR in patients who have not been treated with levodopa before.

4.2 Posology and method of administration

To be taken orally.

‘Sinemet’ CR and Half ‘Sinemet’ CR tablets contain a 1:4 ratio of carbidopa to levodopa (‘Sinemet’ CR: carbidopa 50 mg/levodopa 200 mg, Half ‘Sinemet’ CR 25 mg/100 mg per tablet). 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 and Half ‘Sinemet’ CR may only be administered as whole tablets. So that the controlled release properties of the product can be maintained, tablets should not be chewed, crushed, or halved.

Standard antiparkinson drugs, other than levodopa alone, may be continued while ‘Sinemet’ CR or Half ‘Sinemet’ CR are being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, ‘Sinemet’ CR or Half ‘Sinemet’ CR can be given to patients receiving supplemental pyridoxine (vitamin B6)

Initial Dose

Patients currently treated with conventional levodopa/decarboxylase inhibitor combinations.

Dosage with ‘Sinemet’ CR should be substituted initially at an amount that provides no more than approximately 10% more levodopa per day when higher dosages are given (more than 900 mg per day). The dosing interval between doses should be prolonged by 30 to 50% at intervals ranging from 4 to 12 hours. It is recommended to give the smaller dose, if divided doses are not equal, at the end of the day. The dose needs to be titrated further depending on clinical response, as indicated below under 'Titration'. Dosages that provide up to 30% more levodopa per day may be necessary.

A guide for substitution of ‘Sinemet’ CR treatment for conventional levodopa/decarboxylase inhibitor combinations is shown in the table below:

Guideline for Conversion from Sinemet to Sinemet CR

Sinemet Daily Dosage Levodopa (mg)	Sinemet CR Daily Dosage Levodopa (mg)	Dosage Regimen
300 - 400	400	1 Tablet x 2 daily
500 - 600	600	1 Tablet x 3 daily
700 - 800	800	4 Tablets in 3 or more divided doses
900 - 1000	1000	5 Tablets in 3 or more divided doses
1100 - 1200	1200	6 Tablets in 3 or more divided doses
1300 - 1400	1400	7 Tablets in 3 or more divided doses
1500 - 1600	1600	8 Tablets in 3 or more divided doses

Half ‘Sinemet’ CR is available to facilitate titration when 100 mg steps are required.

Patients currently treated with levodopa alone

Levodopa must be discontinued at least eight hours before therapy with ‘Sinemet’ CR is started. In patients with mild to moderate disease, the initial recommended dose is one tablet of ‘Sinemet’ CR twice daily.

Patients not receiving levodopa

In patients with mild to moderate disease, the initial recommended dose is one tablet of ‘Sinemet’ CR twice daily. Initial dosages should not exceed 600 mg per day of levodopa, nor be given at intervals of less than six hours.

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 two to eight tablets per day of ‘Sinemet’ CR administered as divided doses at intervals ranging from four to twelve hours during the waking day. Higher doses (up to 12 tablets) and shorter intervals (less than four 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 one hour compared with the response usually obtained from the first morning dose of ‘Sinemet’.

An interval of at least three 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 or Half ‘Sinemet’ CR may be required.

Addition of other antiparkinson medication

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

Interruption of therapy

Patients should be observed carefully if abrupt reduction or discontinuation of ‘Sinemet’ CR or Half ‘Sinemet’ CR is required, especially if the patient is receiving antipsychotics (see 4.4 ‘Special Warnings and Precautions for use’).

Use in children

Safety and effectiveness of ‘Sinemet’ CR or Half ‘Sinemet’ CR in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

4.3 Contraindications

‘Sinemet’ CR or Half ‘Sinemet’ CR should not be given when administration of a sympathomimetic amine is contraindicated.

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with ‘Sinemet’ CR or Half ‘Sinemet’ CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with ‘Sinemet’ CR or Half ‘Sinemet’ CR. ‘Sinemet’ CR or Half ‘Sinemet’ CR may be administered concomitantly with the manufacturer’s lowest recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegeline hydrochloride). (See 4.5 ‘Interactions with other medicinal products and other forms of interaction’).

‘Sinemet’ CR or Half ‘Sinemet’ CR is contraindicated in patients with known hypersensitivity to any component of this medication, and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, ‘Sinemet’ CR or Half ‘Sinemet’ CR 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

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least eight hours before therapy with ‘Sinemet’ CR is or Half ‘Sinemet’ CR is started (at least 12 hours if slow-release 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 and Half ‘Sinemet’ CR are not recommended for the treatment of drug-induced extrapyramidal reactions or for the treatment of Huntingdon's chorea.

Based on the pharmacokinetic profile of ‘Sinemet’ CR the onset of effect in patients with early morning dyskinesias may be slower than with conventional ‘Sinemet’. The incidence of dyskinesias is slightly higher during treatment with ‘Sinemet’ CR than with conventional ‘Sinemet’ (16.5% vs 12.2%) in advanced patients with motor fluctuations.

'Sinemet' CR or Half 'Sinemet' CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or with a history of peptic ulcer disease or of convulsions.

Care should be exercised in administering 'Sinemet' CR or Half '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.

As with levodopa, 'Sinemet' CR or Half 'Sinemet' CR may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone or levodopa/decarboxylase inhibitor combination should be observed carefully when 'Sinemet' CR or Half 'Sinemet' CR is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa and use of 'Sinemet' CR or Half 'Sinemet' CR may cause 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.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease.

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 antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of carbidopa-levodopa combinations is reduced abruptly or discontinued, especially if the patient is receiving antipsychotics.

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 and 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.

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

Periodic evaluations of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

If general anaesthesia is required, 'Sinemet' CR or Half '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 medicine.

Melanoma: Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2-to approximately 6-folds 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).

Laboratory Tests: Abnormalities in various laboratory tests have occurred with carbidopa levodopa preparations and may occur with 'Sinemet' CR or Half 'Sinemet' CR. These include elevations of liver function tests such as alkaline phosphatase SGOT (AST), SGPT (ALT), LDH, bilirubin, blood urea nitrogen and positive Coombs test.

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.

Decreased haemoglobin and haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported with standard ‘Sinemet’.

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’ CR or Half ‘Sinemet’ CR:

Antihypertensive agents

Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment of patients receiving some antihypertensive drugs. Therefore when therapy with ‘Sinemet’ CR or Half ‘Sinemet’ CR is started, dosage adjustment of the antihypertensive drug 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 carbidopa-levodopa preparations. (For patients receiving monomine oxidase inhibitors, see 4.3 ‘Contraindications’).

Anticholinergics

Anticholinergics may affect the absorption and thus the patient's response.

Iron

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

Other drugs

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 drugs with ‘Sinemet’ CR or Half ‘Sinemet’ CR should be observed carefully for loss of therapeutic response.

Concomitant therapy with selegeline 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’ CR or Half ‘Sinemet’ CR on the bioavailability of levodopa has not been studied.

4.6 Fertility, pregnancy and lactation

There are insufficient data to evaluate the possible harmfulness of this substance when used in human pregnancy. (See 5.3 ‘Preclinical Safety Data’). 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. ‘Sinemet’ CR or Half ‘Sinemet’ CR should not be given during pregnancy and to nursing mothers.

4.7 Effects on ability to drive and use machines

No data are known about the effect of this product on the ability to drive. Side effects such as dizziness or somnolence may effect the ability to drive or 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 or serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 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:

Cardiovascular: cardiac irregularities, hypertension, phlebitis.

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

Haematologic: leucopenia, 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.

Patients treated with dopamine agonists for treatment of Parkinson's disease, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

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 section 4.3 'Contraindications'). Henoch-Schoenlein purpura. Convulsions have occurred; however, a casual relationship with levodopa or levodopa/carbidopa combinations has not been established.

4.9 Overdose

Management of acute overdosage with 'Sinemet' CR or Half 'Sinemet' CR is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of 'Sinemet' CR.

Electrocardiographic monitoring should be instituted and the patient observed carefully for the 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 or Half 'Sinemet' CR 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

'Sinemet' CR and Half 'Sinemet' CR are a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, in a polymer-based controlled-release tablet formulation, for use in the treatment of Parkinson's disease. 'Sinemet' CR and Half 'Sinemet' CR are particularly useful to reduce 'off' time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had dyskinesias and motor fluctuations.

Patients with Parkinson's disease treated with preparations containing levodopa may develop motor fluctuations characterised by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ('on-off' phenomenon) is characterised by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

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 only the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine. This normally obviates the necessity for large doses of levodopa at frequent intervals. The lower dosage reduces or may help eliminate gastrointestinal and cardiovascular side-effects, especially those which are attributed to dopamine being formed in extracerebral tissues.

'Sinemet' CR and Half 'Sinemet' CR are designed to release their active ingredients over a four-six 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', as established in healthy volunteers.

In clinical trials, patients with motor fluctuations experienced reduced 'off'-time with 'Sinemet' CR when compared with 'Sinemet'. The reduction of the 'off'-time is rather small (about 10%) and the incidence of dyskinesias increases slightly after administration of 'Sinemet' CR compared to standard 'Sinemet'. Global ratings of improvement and activities of daily living in the 'on' and 'off' state, as assessed by both patient and physician, were better during therapy with 'Sinemet' CR than with 'Sinemet'. Patients considered 'Sinemet' CR to be more helpful for their clinical fluctuations, and preferred it over 'Sinemet'. In patients without motor fluctuations, 'Sinemet' CR under controlled conditions, provided the same therapeutic benefit with less frequent dosing than with 'Sinemet'. Generally, there was no further improvement of other symptoms of Parkinson's disease.

5.2 Pharmacokinetic properties

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 percent 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 percent, the daily dosage of levodopa in the controlled release formulation will usually be higher that with conventional formulations. There was no evidence that 'Sinemet' CR released its ingredients in a rapid or uncontrolled fashion.

The pharmacokinetics of levodopa following administration of Half 'Sinemet' CR were studied in patients with Parkinson's disease. Chronic three month, open-label, twice daily dosing with Half 'Sinemet' CR (range: 50 mg carbidopa, 200 mg levodopa up to 150 mg carbidopa, 600 mg levodopa per day) did not result in accumulation of plasma levodopa. The dose-adjusted bioavailability for one Half 'Sinemet' CR tablet was equivalent to that for one 'Sinemet' CR tablet. The mean peak concentration of levodopa following administration of one Half 'Sinemet' CR tablet was approximately 50% greater than that following one 'Sinemet' CR tablet. Mean time-to-peak plasma levels may be slightly less for Half 'Sinemet' CR than for 'Sinemet' CR.

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

5.3 Preclinical safety data

The medicine has appeared harmful in animal trials (visceral and skeletal malformations in rabbits). For reproductive toxicity, see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hyprolose
Magnesium Stearate
Poly (vinyl acetate-crotonic acid) copolymer
Quinoline yellow on aluminium hydride (E104)
Red iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the blister strips and outer carton of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package to protect from light

6.5 Nature and contents of container

Over-labelled cartons containing 3 blister strips (10 tablets per strip).
Pack size 30 tablets

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

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Ltd
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PAA 1447/16/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2009

10 DATE OF REVISION OF THE TEXT