AUSTRALIAN PRODUCT INFORMATION

SINEMET® CR 200/50 (levodopa and carbidopa) Tablet

1 NAME OF THE MEDICINE

Levodopa and carbidopa

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Carbidopa
Carbidopa, an inhibitor of aromatic amino acid decarboxylase, is a white, crystalline compound, slightly soluble in water.

Levodopa
Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

SINEMET CR 200/50 (levodopa 200 mg and carbidopa 50 mg) is supplied as tablets for oral administration. SINEMET CR 200/50 is a controlled-release formulation of levodopa, and carbidopa, in a ratio of 4:1. The tablet contains a polymer-based drug delivery system which controls the release of levodopa and carbidopa as it slowly erodes.

SINEMET CR 200/50 is a peach-coloured, oval shaped, biconvex tablet, deep scored on one side and the other marked '521'.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Idiopathic parkinsonism, where standard formulations containing levodopa/carbidopa have produced inadequate control. Experience is limited with SINEMET CR 200/50 in patients who have not been treated with levodopa before.

4.2 DOSE AND METHOD OF ADMINISTRATION

SINEMET CR 200/50 tablets contain a 4:1 ratio of levodopa to carbidopa (levodopa 200 mg/carbidopa 50 mg per tablet). The daily dosage of SINEMET CR 200/50 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.

The tablets must NOT be broken and should be taken as a whole.

SINEMET CR 200/50 should only be administered as whole tablets. So that the controlled release properties of the product can be maintained, tablets should not be chewed or crushed.

Standard antiparkinson drugs, other than levodopa alone, may be continued while SINEMET CR 200/50 is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR 200/50 can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage

Patients Currently Treated with Conventional Levodopa/Decarboxylase Inhibitor Combinations.
Dosage with SINEMET CR 200/50 should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see **Section 4.2 Dose and Method of Administration, Titration**). The interval between doses of SINEMET CR 200/50 should be 4-8 hours during the waking day. (See **Section 5.2 Pharmacokinetic Properties**).

A guide for substitution of SINEMET CR 200/50 treatment for conventional levodopa/ decarboxylase inhibitor combinations is shown in the table below

Table 1.
Guidelines for Initial Conversion from Levodopa/decarboxylase inhibitor to SINEMET CR 200/50

LEVODOPA/DECARBOXYLASE INHIBITOR	**SINEMET CR 200/50**
Total Daily Dose* Levodopa (mg)	Example Dosage Regimen
300 - 400	1 tab b.i.d.
500 - 600	1 tab t.i.d.
700 - 800	A total of 4 tabs in 4 divided doses.
900 - 1000	A total of 5 tabs in 3 or more divided doses (eg. 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

* For dosing ranges not shown in the table see **Section 4.2 Dose 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 eight hours before therapy with SINEMET CR 200/50 is started. In patients with mild to moderate disease, the initial recommended dose is one tablet of SINEMET CR 200/50 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 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 (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR 200/50 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 200/50 may be required.

Addition of Other Antiparkinson Medications

Anticholinergic agents, dopamine agonists and amantadine can be given with SINEMET CR 200/50. Dosage adjustment of SINEMET CR 200/50 may be necessary when these agents are added to an existing treatment regimen for SINEMET CR 200/50.

A dose of SINEMET 100/25 can be added to the dosage regimen of SINEMET CR 200/50 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 200/50 is required, especially if the patient is receiving neuroleptics (see **Section 4.4 Special Warnings and Precautions for Use**).

If general anaesthesia is required, SINEMET CR 200/50 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.

4.3 CONTRAINDICATIONS

Monoamine oxidase inhibitors and SINEMET CR 200/50 should not be given concomitantly. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR 200/50. SINEMET CR 200/50 may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B, eg selegiline (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, Other drugs**).

SINEMET CR 200/50 is contraindicated in patients with known hypersensitivity and in patients with narrow angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR 200/50 should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least 8 hours before therapy with SINEMET CR 200/50 is started (at least 12 hours if slow-release plain levodopa has been administered).

The tablets must NOT be broken and should be taken as a whole.

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.

As with levodopa, SINEMET CR 200/50 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.

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.

SINEMET CR 200/50 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 200/50 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 200/50, 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 antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of levodopa-carbidopa combinations is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

SINEMET CR 200/50 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 200/50 for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).

Compulsive behaviour

Patient 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, medication use and punding (repetitive purposeless activity)) have been reported in patients treated with dopamine agonists and/or other dopaminergic treatment for Parkinson's disease, especially at high doses. Review of treatment is recommended if such symptoms develop. Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences.

Use in hepatic impairment

SINEMET CR 200/50 should be administered cautiously to patients with severe hepatic disease. Periodic evaluation of hepatic function is recommended during extended therapy.

Use in renal impairment

SINEMET CR 200/50 should be administered cautiously to patients with severe renal disease. Periodic evaluation of renal function is recommended during extended therapy.

Use in the elderly

There is wide experience in the use of levodopa and carbidopa in elderly patients. The recommendations set out above reflect the clinical data derived from this experience (see sections 4.2 **Dose and Method of Administration** and 5.2 **Pharmacokinetic Properties).**

Paediatric use

Safety and effectiveness of SINEMET CR 200/50 in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

Effects on laboratory tests

Laboratory tests which have been reported to be abnormal are creatinine, uric acid, alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, and Coombs' test.

Decreased haemoglobin and 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.

In some patients in clinical studies a minor elevation of blood glucose (not above 5% range) was noted. This may be the effect of high dose levodopa on glucose tolerance and may not have clinical significance.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR 200/50:

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 200/50 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 monoamine oxidase inhibitors, see **Section 4.3 Contraindications**.

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

Other Drugs:
Dopamine D_2 receptor antagonists (eg. 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 200/50 should be observed carefully for loss of therapeutic response.

Use of SINEMET CR 200/50 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 Contraindications**).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In reproduction studies with levodopa and carbidopa, 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 human dose of levodopa.

Therefore, the use of SINEMET CR 200/50 in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Use in pregnancy (Category B3)

Although the effects of SINEMET CR 200/50 on human pregnancy are unknown, both levodopa and combinations of levodopa and carbidopa have caused visceral and skeletal malformations in rabbits. Therefore, use of SINEMET CR 200/50 in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Use in 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 drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, SINEMET CR 200/50 should not be used by nursing mothers. A

decision should be made either to discontinue nursing or to discontinue SINEMET CR 200/50.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

See **Section 4.4 Special Warnings and Precautions for Use.**

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In controlled clinical trials in patients with moderate to severe motor fluctuations SINEMET CR 200/50 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 somewhat greater incidence of dyskinesias was seen with SINEMET CR 200/50 than with SINEMET possibly due to the replacement of "off" time (which is reduced with SINEMET CR 200/50) by "on" time (which is sometimes accompanied by dyskinesias). Patients with motor fluctuations receiving SINEMET CR 200/50 may develop dyskinesias more often at higher doses (over 1500 mg of levodopa daily) in association with a decrease in "off-time".

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, somnolence, insomnia, depression, asthenia, vomiting and anorexia.

Other side effects reported in post-marketing experience or observed rarely (0.5 - 1%) in clinical trials include:

Body as a whole: chest pain, syncope.

Cardiovascular: palpitation, orthostatic effects including hypotensive episodes.

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

Hypersensitivity: angioedema, urticaria, pruritus.

Investigations: weight gain, weight loss.

Metabolism and nutrition disorders: anorexia.

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, muscle cramps, on-off phenomenon, peripheral neuropathy, psychotic episodes including delusions and paranoid ideation.

Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

In post-marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating have been reported with dopamine agonists and/or other dopaminergic treatments, and in patients treated with levodopa including SINEMET CR 200/50 (see **Section 4.4 Special Warnings and Precautions for Use**).

Respiratory: dyspnoea.

Skin: flushing, alopecia, rash, dark sweat.

Special Senses: blurred vision.

Urogenital: dark urine, urinary tract infection.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with "SINEMET" CR 200/50 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, sleepiness, euphoria and dementia, depression with suicidal tendencies.

Skin: increased sweating.

Special Senses: diplopia, dilated pupils, oculogyric crises.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: oedema, weakness, faintness, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see **Section 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 effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Management of acute overdosage with SINEMET CR 200/50 is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET CR 200/50.

In the event of overdosage, 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 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 200/50 should be taken into consideration. To date, no experience has been reported with dialysis, hence its value in overdosage is not known.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Parkinson's disease is a degenerative neurological disorder characterised by the progressive loss of dopaminergic nigrostriatal neurons. The signs and symptoms, including rigidity, tremor, bradykinesia, postural changes, and gait disturbances, are usually treated adequately with drugs that mimic or replace depleted dopamine. SINEMET CR 200/50, which combines the dopamine precursor, levodopa, and the peripheral levodopa/decarboxylase inhibitor, carbidopa, is effective in providing dopamine to the brain. Carbidopa, which does not cross the blood-brain barrier, increased both plasma levels and plasma half-life of levodopa by inhibiting extracerebral levodopa/decarboxylation, principally in the intestinal mucosa.

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.

SINEMET CR 200/50 contains 200 mg of levodopa and 50 mg of carbidopa in a controlled-release dosage form designed to release these ingredients over a 4 to 6 hour period. With this formulation there is less variation in plasma levodopa levels than with conventional SINEMET.

Clinical trials

In clinical trials, patients with moderate to severe motor fluctuations who received SINEMET CR 200/50 experienced reduced ''off'' time when compared with 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 200/50 than with SINEMET. Patients considered SINEMET CR 200/50 to be more helpful for their motor fluctuations, and preferred it over SINEMET. In patients without motor fluctuations, SINEMET CR 200/50, under controlled conditions, provided the same therapeutic benefit with less frequent dosing when compared with SINEMET.

5.2 PHARMACOKINETIC PROPERTIES

Carbidopa

Absorption

Following an oral dose of radioactive labelled carbidopa to healthy subjects and to patients with Parkinson's disease, maximum plasma levels of radioactivity were reached in two to four hours in the normal subjects and in one and one-half to five hours in the patients.

Metabolism and Excretion

Following an oral dose of radioactive labelled carbidopa to healthy subjects and to patients with Parkinson's disease, approximately equal quantities were excreted in the urine and the faeces

by both groups. Comparison of urinary metabolites in healthy subjects and patients indicated that the drug is metabolised to the same degree in both. Urinary excretion of unchanged drug was essentially complete in seven hours and represented 35 percent of the total urinary radioactivity. Only metabolites were present thereafter.

Among the metabolites excreted by man are alpha-methyl-3-methoxy-4-hydroxy-phenylpropionic acid and alpha-methyl-3, 4-dihydroxyphenylpropionic acid. These accounted for approximately 14 and 10 percent, respectively, of the radioactive metabolites excreted. Two minor metabolites were found. One was identified as 3, 4-dihydroxy-phenyl-acetone and the other tentatively identified as N-methyl-carbidopa. They each accounted for less than five percent of the urinary metabolites. Unchanged carbidopa also was present in the urine. No conjugates were found.

Levodopa

Absorption

Levodopa is absorbed rapidly from the gastrointestinal tract.

Metabolism and Excretion

Levodopa is extensively metabolised. Although more than 30 metabolites may be formed, it is converted mainly to dopamine, epinephrine and norepinephrine, and eventually to dihydroxyphenylacetic acid, homovanillic acid and vanillylmandelic acid. 3-O-methyldopa appears in the plasma and cerebrospinal fluid. Its significance is not known.

When single test doses of radioactive levodopa are given to fasting patients with Parkinson's disease, plasma levels of radioactivity reach a peak level in one-half to two hours and remain measurable for four to six hours. At peak levels, about 30% of radioactivity appears as catecholamines, 15% as dopamine, and 10% as dopa.

Radioactive compounds are excreted rapidly in the urine, one-third of the dose appearing in two hours. Eighty to ninety percent of urinary metabolites are phenylcarboxylic acids, principally homovanillic acid. Over 24 hours, one or two percent of recovered radioactivity is dopamine, and less than one percent is epinephrine, norepinephrine, and unchanged levodopa.

Effect of carbidopa on levodopa metabolism

In healthy subjects carbidopa increased plasma levels of levodopa consistently by statistically significant amounts, measured against placebo. This has been demonstrated when carbidopa was given before levodopa and when the two drugs were given simultaneously. In one study, pretreatment with carbidopa increased plasma levels of a single dose of levodopa about five times and extended the duration of measurable plasma concentrations of levodopa from four hours to eight hours. When the two drugs were given simultaneously in other studies, similar results were obtained.

In a study in which a single dose of stem-labelled levodopa was given to patients with Parkinson's disease who had been pretreated with carbidopa, there was an increase in the half-life of total plasma radioactivity derived from the levodopa, from 3 hours to 15 hours. The proportion of radioactivity remaining as unmetabolised levodopa was increased at least three times by carbidopa. Plasma and urinary dopamine and homovanillic acid were both decreased by carbidopa pretreatment.

Pharmacokinetics of SINEMET CR 200/50

The pharmacokinetics of levodopa following administration of SINEMET CR 200/50 were studied in young and elderly healthy volunteers. The mean time to peak plasma levodopa level after SINEMET CR 200/50 was approximately two hours compared to 0.75 hours with SINEMET. The mean peak plasma levodopa levels were 60 percent lower with SINEMET CR 200/50 than with SINEMET. The *in vivo* absorption of levodopa following administration of SINEMET CR 200/50 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 200/50, relative to SINEMET, is approximately 70 percent, 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 200/50 released its ingredients in a rapid or uncontrolled fashion.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Please see **Carcinogenicity** subsection below**.**

Carcinogenicity

In a two-year bioassay with levodopa and carbidopa, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

In addition to the active ingredients levodopa and carbidopa, each tablet contains the following inactive ingredients: hyprolose, magnesium stearate,VA/Crotonates copolymer, quinoline yellow aluminium lake, ferric oxide.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep in tightly closed container, protected from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

SINEMET CR 200/50 is supplied in HDPE bottles with a polypropylene CRC closure of 100 tablets - AUST R 326195.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

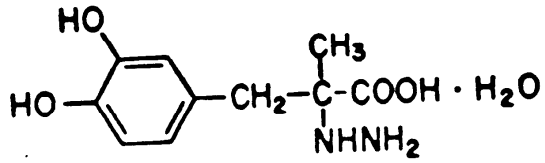
Carbidopa
The empirical formula is $C_{10}H_{14}N_2O_4$ with a molecular weight of 244.3. It is designed chemically as (-)-L-alpha-hydrazino-alpha-methyl-beta-(3,4-dihydroxy-benzene) propanoic acid monohydrate. Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa
The empirical formula is $C_9H_{11}NO_4$ with a molecular weight of 197.2. It is designated chemically as (-)-L-alpha-amino-beta-(3, 4-dihydroxybenzene) propanoic acid.

Chemical structure

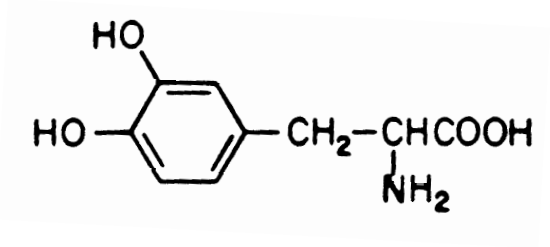
Carbidopa

The structural formula is:



Levodopa

The structural formula is:



CAS number

Carbidopa: 28860-95-9
Levodopa: 59-92-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Organon Pharma Pty Ltd
Building A, 26 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

13 April 2011

10 DATE OF REVISION

15 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Addition of post-marketing Adverse event UTI

S-IPC-OG0295B-CR-062023

RCN 100003042-AU