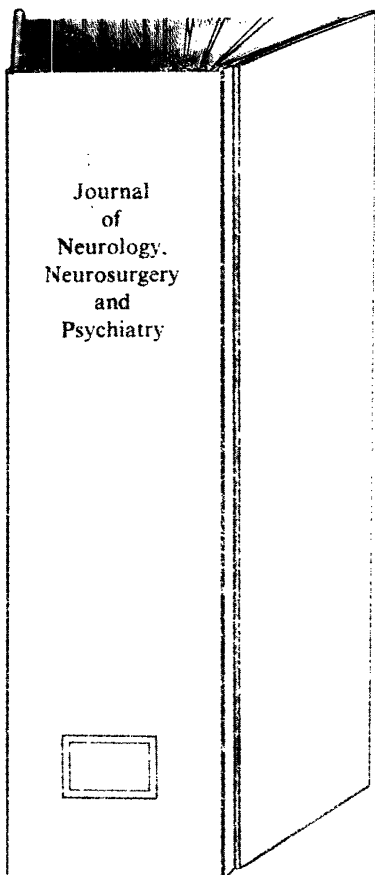


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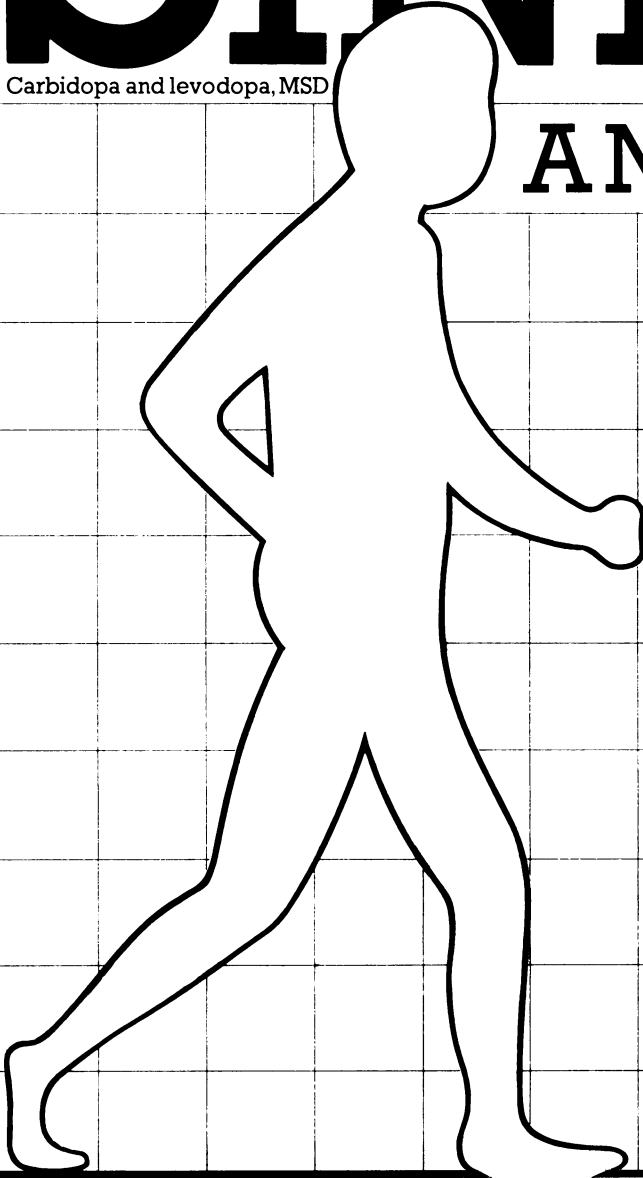
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For prescribing information, see overleaf.

## PRESCRIBING INFORMATION

### INDICATIONS

For treatment of Parkinson's disease and syndrome.

### DOSE AND ADMINISTRATION

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

'Sinemet' Tablets are available as:

'Sinemet-110 containing 10 mg carbidopa and 100 mg levodopa.

'Sinemet-Plus' containing 25 mg carbidopa and 100 mg levodopa.

'Sinemet-275 containing 25 mg carbidopa and 250 mg levodopa.

**General considerations:** Studies show that the peripheral enzyme dopa decarboxylase is fully inhibited (saturated) by carbidopa at doses between 70 and 100 mg a day. 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.

Patients who require less than 700 mg levodopa given as 'Sinemet-275 will theoretically not receive sufficient carbidopa to saturate peripheral dopa decarboxylase. 'Sinemet-Plus' may be helpful, especially for patients with nausea and vomiting.

Most patients can be maintained on divided doses of three to six tablets of 'Sinemet-275 a day. Tablets are scored for easy division should the frequency of daily dosage need to be increased. During the titration period, 'Sinemet-Plus' may be more convenient.

Patients on 'Sinemet-Plus' who need a higher dosage should be switched to 'Sinemet-275. Dosage with either form should not exceed eight tablets a day. If patients do show a need for higher doses, levodopa should be added.

Because both beneficial and adverse effects are seen more rapidly with 'Sinemet' than with levodopa, patients should be carefully monitored during the dosage adjustment period. Involuntary movements, particularly blepharospasm, is a useful early sign of excess dosage in some patients.

'Sinemet-110 can be used as an alternative to 'Sinemet-Plus'.

**Patients not receiving levodopa:** Dosage may be initiated with one tablet of 'Sinemet-Plus' three times a day, and adjusted as necessary by small increments to a maximum daily dosage of eight tablets. If patients need more levodopa, one tablet of 'Sinemet-275 should be substituted three or four times a day. If further titration is necessary, the dosage of 'Sinemet-275 may be increased gradually to a maximum of eight tablets a day.

**Patients receiving levodopa:** Discontinue levodopa at least twelve hours (24 hours for slow-release preparations) before starting therapy with 'Sinemet'. The easiest way to do this is to give 'Sinemet' as the first morning dose after a night without any levodopa. The dose of 'Sinemet' should be approximately 20% of the previous daily dosage of levodopa.

The suggested starting dose for most patients is one tablet of 'Sinemet-275 three or four times a day.

Patients requiring less than 1,500 mg levodopa a day should be started on one tablet of 'Sinemet-Plus' three or four times a day.

The dosage may then be adjusted gradually, but should not exceed eight tablets a day.

**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 twelve 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/decaboxylase inhibitor combination.

**Use with other antiparkinsonian agents:** Current evidence indicates that other antiparkinsonian agents such as anticholinergics and amantadine may be continued when 'Sinemet' is introduced, although dosage may have to be adjusted.

### CONTRA-INDICATIONS

Concurrent use with monoamine oxidase inhibitors (these must be discontinued at least two weeks before starting 'Sinemet'); narrow-angle glaucoma; known hypersensitivity to this medication. Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

See also 'Use in pregnancy and the nursing mother', under 'Precautions'.

### PRECAUTIONS

'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. All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with current psychoses should be treated with caution. 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. If concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones is necessary, such drugs should be administered with caution, and patients carefully observed for loss of antiparkinsonian effect. Patients with a history of convulsions should be treated with caution. Both phenytoin and papaverine have been reported to reverse the beneficial effects of levodopa.

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 atrial, nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.

As symptoms of postural hypotension have occasionally been reported, 'Sinemet' should be given with caution to patients receiving antihypertensive agents. Adjustment of the dosage of the antihypertensive agent may be required when 'Sinemet' is started. (For patients on pargyline, see the contra-indication on monoamine oxidase inhibitors.)

As with levodopa there is a possibility of upper gastrointestinal haemorrhage in patients with a history of peptic ulcer.

If general anaesthesia is required, therapy with 'Sinemet' may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

Transient abnormalities in laboratory test results may occur, but have not been associated with clinical evidence of disease. These include elevated levels of blood urea, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase, or protein-bound iodine.

Positive Coombs tests have been reported, both with 'Sinemet' and levodopa alone, but haemolytic anaemia is extremely rare.

**Use in children:** The safety of 'Sinemet' in patients under eighteen years of age has not been established.

**Use in pregnancy and the nursing mother:** Although the effects of 'Sinemet' on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Therefore, use of 'Sinemet' in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur. 'Sinemet' should not be given to nursing mothers.

**Drug interactions:** Clinical experience with concurrent administration of 'Sinemet' and other standard antiparkinsonian drugs, e.g. benzotropine mesylate, benzhexol hydrochloride, is limited. To date, however, there has been no indication of interactions that would preclude concurrent use. No adverse reactions have been reported that do not occur with the various agents alone.

### SIDE EFFECTS

Side effects that occur frequently with 'Sinemet' are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by dosage reduction. The most common are choreiform, dystonic, and other involuntary movements. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

Less common are mental changes, including paranoid

(Prescribing Information Cont)

ideation and psychotic episodes; depression, with or without development of suicidal tendencies; and dementia. Convulsions have occurred, but a causal relationship has not been established.

Less frequent side effects are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, nausea, vomiting, and dizziness.

Gastro-intestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, leucopenia, and agranulocytosis have occurred rarely.

Positive Coombs tests have been reported both with 'Sinemet' and with levodopa alone, but haemolytic anaemia is extremely rare.

Other side effects that have been reported include:

**Psychiatric:** euphoria, lethargy, sedation, stimulation, fatigue and malaise, confusion, insomnia, nightmares, hallucinations and delusions, agitation and anxiety.

**Neurological:** ataxia, faintness, headache, increased hand tremor, trismus, oculogyric crisis, weakness, numbness, bruxism.

**Gastro-intestinal:** constipation, diarrhoea, epigastric and abdominal distress and pain, flatulence, hiccups, sialorrhoea, difficulty in swallowing, bitter taste, dry mouth, burning sensation of the tongue.

**Dermatological:** sweating, oedema, hair loss, rash, unpleasant odour, dark sweat.

**Respiratory:** hoarseness, bizarre breathing pattern.

**Urogenital:** urinary retention, incontinence, haematuria, dark urine, priapism.

**Special senses:** blurred vision, diplopia, dilated pupils, activation of latent Homer's syndrome.

**Other:** hot flushes, weight gain or loss, flushing, abnormalities in laboratory tests (see 'Precautions').

**PRESENTATION**

There are three strengths of 'Sinemet':

The standard strength is known as 'Sinemet-275' and is supplied as dapple-blue, half-scored, oval tablets, marked 'MSD 654'; containing 25 mg carbidopa (as carbidopa monohydrate) and 250 mg levodopa BP, in bottles of 100.

'Sinemet-Plus' is available as yellow, half-scored, oval tablets, marked 'SINEMET-PLUS'; containing 25 mg carbidopa (as carbidopa monohydrate) and 100 mg levodopa BP, in bottles of 100 and 1,000.

'Sinemet-110', supplied as dapple-blue, half-scored, oval tablets, marked 'MSD 647'; containing 10 mg carbidopa (as carbidopa monohydrate) and 100 mg levodopa BP, in bottles of 100.

Basic NHS costs:

'Sinemet-275' Tablets (100) £12.20.  
'Sinemet-Plus' Tablets (100) £10.70.  
'Sinemet-110' Tablets (100) £6.30.

Product licence numbers:

'Sinemet-275' Tablets, 0025/0085.  
'Sinemet-Plus' Tablets, 0025/0150.  
'Sinemet-110' Tablets, 0025/0084.

Product authorisation numbers:

'Sinemet-275' Tablets, 35/47/2.  
'Sinemet-Plus' Tablets, 35/47/3.  
'Sinemet-110' Tablets, 35/47/1.


Agents in the Republic of Ireland:

Cahill May Roberts, P.O. Box 1090, Chapelizod, Dublin 20.

Additional information is available to the medical profession on request.

Issued September 1981.

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