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*From:* The Subscription Manager, JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY BMA House, Tavistock Square, London WClH 9JR
'Sinemet-Plus' contains 100 mg of levodopa and 25 mg of carbidopa. 'Sinemet-Plus' provides a low dose of levodopa together with sufficient carbidopa to inhibit effectively peripheral dopa-decarboxylase in many patients. It retains the advantage of co-prescribing carbidopa and levodopa by reducing or eliminating certain levodopa side effects, e.g. GI upsets, etc.

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The addition of 'Sinemet-Plus' to the 'Sinemet' range means that Parkinsonian patients may benefit from levodopa therapy earlier and be eased more gradually into the full-scale therapy offered by Sinemet®110 and Sinemet®275.

**SINEMET-Plus™**

**A new start for many Parkinsonian patients**

For prescribing information, see overleaf.
INDICATIONS
For treatment of Parkinson's disease and syndrome.

DOSEAGE 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 carbipoda and 100 mg levodopa. Sinemet®Plus containing 25 mg carbipoda and 100 mg levodopa. Sinemet®28 containing 25 mg carbipoda and 250 mg levodopa.

General considerations: Studies show that the peripheral enzyme dopa decarboxylase is fully inhibited (saturated) by carbipoda at doses between 70 and 100 mg a day. The formulations of Sinemet are designed to provide a range of doses with sufficient carbipoda to inhibit peripheral dopa decarboxylase and thus exert optimal therapy. Doses less than 700 mg levodopa given as Sinemet®285 will therapeutically not receive sufficient carbipoda 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®285 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®285. Dosage with either form should not exceed eight tablets a day. If patients do show a need for higher dosage, 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®285 should be substituted three or four times a day. If further titration is necessary the dosage of Sinemet®285 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 90% of the previous daily dosage of levodopa. The suggested starting dose for most patients is one tablet of Sinemet®285 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/ decarboxylase 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.

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 antipsychotic behaviour. Patients with current psychoses should be treated with caution. Patients with a history of severe involuntary movements or psychotonic 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®. 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, SCOT, 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 carbipoda 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. benzphetamine maleate, 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, explosive 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.

I. 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 hypotension episodes, bradycardiac episodes (the "on-off" phenomenon), anorexia, nausea, vomiting, and dizziness.

Gastro-intestinal bleeding, development of duodenal ulcer, hypertension, phebitis, 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, tinnitus, oculogyric crisis, weakness, numbness, bruxism.

**Gastro-intestinal:** constipation, diarrhoea, epigastric and abdominal distress and pain, flatulence, hiccups, salorrhoea, 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' 2575 and is supplied as dapple-blue, half-scored, oval tablets, marked MSD 694 containing 25 mg carbodopa (as carbodopa monohydrate) and 200 mg levodopa BP in bottles of 100.
- 'Sinemet-Pi' is available as yellow, half-scored, oval tablets, marked SINEMET-PLUS containing 25 mg carbodopa (as carbodopa monohydrate) and 100 mg levodopa BP in bottles of 100 and 1,000.
- 'Sinemet-110' is supplied as dapple-blue, half-scored, oval tablets, marked MSD 647 containing 10 mg carbodopa (as carbodopa monohydrate) and 100 mg levodopa BP in bottles of 100.

- Basic NHS costs:
  - Sinemet Tablets (100) £12.20
  - Sinemet-Pi Tablets (100) £10.70
  - Sinemet-110 Tablets (100) £8.30

- Product licence numbers:
  - Sinemet Tablets, O025/0065.
  - Sinemet-PLUS Tablets, 0025/0150.
  - Sinemet-110 Tablets, 0025/0084

- Product registration numbers:
  - Sinemet Tablets, 35/47/2.
  - Sinemet-PLUS Tablets, 35/47/3.
  - Sinemet-110 Tablets, 35/47/4.

- Agents in the Republic of Ireland:
  - Cahill May Roberts P.C. Box 1096, Chapelizod, Dublin 20.

- Additional information is available to the medical profession on request.

Issued September 1981.

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