SINEMET® & SINEMET® CR
Carbidopa/levodopa

PRESENTATION

Sinemet 12.5 mg/50 mg Tablets contains 12.5 mg of anhydrous carbidopa and 50 mg levodopa.

Sinemet 10 mg/100 mg Tablets contains 10 mg of anhydrous carbidopa and 100 mg levodopa.

Sinemet Plus 25 mg/100 mg Tablets contains 25 mg of anhydrous carbidopa and 100 mg levodopa.

Sinemet 25 mg/250 mg Tablets contains 25 mg of anhydrous carbidopa and 250 mg levodopa.

Sinemet CR 50 mg/200 mg Prolonged-Release Tablets contains 50 mg of anhydrous carbidopa and 200 mg levodopa.

Half Sinemet CR 25 mg/100 mg Prolonged-Release Tablets contains 25 mg of anhydrous carbidopa and 100 mg levodopa.

USES

Antiparkinsonian agent.

Sinemet (excluding Sinemet CR & Half Sinemet CR)
For treatment of Parkinson’s disease and syndrome.

Sinemet CR & Half Sinemet CR
Idiopathic Parkinson’s disease, in particular to reduce off-period in patients previously treated with levodopa/decarboxylase inhibitors, or with levodopa alone and who have experienced motor fluctuations. Experience is limited with Sinemet CR and Half Sinemet CR in levodopa-naïve patients.

DOSAGE AND ADMINISTRATION

Consult the Summary of Product Characteristics.

Oral use. Use in patients below the age of 18 is not recommended.

Sinemet (excluding Sinemet CR & Half Sinemet CR): The optimum daily dose must be determined by careful titration. Sinemet tablets are available in a ratio of 1:4 or 1:10 of carbidopa to levodopa to provide a facility for fine dosage titration. Dopa-decarboxylase is
fully inhibited (saturated) by carbidopa at doses between 70 and 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Standard antiparkinsonian drugs, other than levodopa alone, may be continued while Sinemet/Sinemet CR/Half Sinemet CR are being administered, although their dosage may have to be adjusted. Monitor carefully during the dosage adjustment period. Involuntary movements, particularly blepharospasm, are a useful early sign of excess dosage.

**Patients not receiving levodopa:** Dosage may be best initiated with one tablet of Sinemet Plus t.d.s (three times a day). Dosage may be increased by one tablet of Sinemet 12.5 mg/50 mg or Sinemet Plus every day or every other day, as necessary, until a dosage equivalent of 8 tablets of Sinemet Plus a day is reached. If Sinemet 10 mg/100 mg or Sinemet 12.5 mg/50 mg is used, dosage may be initiated with one tablet t.d.s or q.d.s. (four times a day). Titration upwards may be required. Dose may be increased by one tablet every day or every other day until a total of 8 tablets (2 tablets q.d.s.) is reached. Fully effective doses usually are reached within 7 days. Sinemet 12.5 mg/50 mg or Sinemet 10 mg/100 mg may be used to facilitate individual dosage titration.

**Patients receiving levodopa:** Discontinue levodopa at least 12 hours (24 hours for slow-release preparations) before starting therapy with Sinemet. The dose of Sinemet should be approximately 20% of the previous daily dosage of levodopa. Patients taking less than 1,500 mg levodopa a day should take one tablet of Sinemet Plus t.d.s. or q.d.s. dependent on need. Suggested starting dose for most patients taking more than 1,500 mg levodopa a day is one tablet of 'Sinemet 25 mg/250 mg' t.d.s. or q.d.s.

**Maintenance:** Therapy with Sinemet should be individualised and adjusted gradually according to response. Experience with a total daily dosage greater than 200 mg carbidopa is limited.

**Patients receiving levodopa with another decarboxylase inhibitor:** Discontinue dosage at least 12 hours before Sinemet is started. The initial dosage of Sinemet should provide the same levodopa dose as contained in the existing levodopa/decarboxylase inhibitor combination.

Sinemet CR & Half Sinemet CR
May only be administered as whole tablets. To maintain the controlled release properties of the product, 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 dose may have to be adjusted. Sinemet CR or Half Sinemet CR can be given to patients receiving supplemental pyridoxine (vitamin B6).

**Patients currently treated with conventional levodopa/decarboxylase inhibitor combinations:** When higher doses are given (more than 900 mg per day) Sinemet CR should be substituted at an initial dose providing no more than approximately 10% more levodopa per day. The dosing interval 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. Titrate dose in line with clinical response. Please see Summary of Product Characteristics for details of dose titration, and conversion of Sinemet to Sinemet CR and Half Sinemet CR.
Patients currently treated with levodopa alone: Discontinue levodopa at least 8 hours before Sinemet CR is started. For patients with mild to moderate disease, the initial recommended dose is one tablet of Sinemet CR b.d.

Patients not receiving levodopa: In patients with mild to moderate disease, the initial dose is one tablet of Sinemet CR b.d. Initial dose of levodopa, should not exceed 600 mg per day and should be given at intervals of less than six hours.

Titration: Following initiation, doses and dosing intervals may be varied depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets per day of Sinemet CR given at divided doses of 4 to 12 hours during the waking day. Doses of up to 12 tablets per day over shorter intervals are not recommended. When given at intervals of less than 4 hours, or if the divided doses are unequal, the smaller doses should be given at the end of the day. An interval of at least three days between dosage adjustments is recommended.

Maintenance: Periodic clinical evaluation is recommended. Dosage adjustment may be required. Patients should be observed carefully if abrupt reduction or discontinuation is required, especially if the patient is receiving antipsychotics.

Addition of other antiparkinson medication: Sinemet CR or Half Sinemet CR - Anticholinergic agents, dopamine agonists and amantadine can be given with Sinemet CR or Half Sinemet CR. Dosage adjustment may be required. Sinemet (excluding Sinemet CR & Half Sinemet CR) - Other antiparkinsonian agents may be continued. Dose adjustment may be required.

CONTRA-INDICATIONS
Sinemet, Sinemet CR and Half Sinemet CR
Non-selective MAO inhibitors. These inhibitors must be discontinued at least 2 weeks before starting dosing (may be co-administered with the manufacturer’s recommended dose of MAO Type B selective inhibitors). Patients with narrow-angle glaucoma, known hypersensitivity to any component of this medication, suspicious undiagnosed skin lesions or a history of melanoma, patients with severe psychoses.

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

PRECAUTIONS
Monitor carefully for the development of mental changes, depression with suicidal tendencies, and other serious anti-social behaviour. Patients with psychoses should be treated with caution. Not recommended for the treatment of drug-induced extrapyramidal reactions. Dyskinesias may occur in patients previously treated with levodopa alone and may require dosage reduction. Administer with caution to patients: with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease. In patients with a history of myocardial infarction who have residual, atrial, nodal, or ventricular arrhythmias, cardiac function should be monitored during the period of initial dosage adjustment and titration. 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. A reduction in dose or termination of therapy may be considered. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone should be observed carefully. Dose 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. An abrupt dose reduction or withdrawal of Sinemet should be carefully observed, particularly in patients who are also receiving neuroleptics or antipsychotics. Monitor regularly for development of impulse control disorders; behavioural symptoms are: pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating. 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. Periodic evaluation of hepatic, haematopoetic, cardiovascular and renal function are recommended during extended therapy. Monitor for melanomas on a regular basis. Patients with a history of convulsions should be treated with caution.

**Sinemet CR and Half Sinemet CR only**

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least 8 hours before therapy with Sinemet CR or Half Sinemet CR is started (at least 12 hours if slow-release levodopa has been administered). The onset of effect in patients with early morning dyskinesias may be slower than with conventional 'Sinemet'.

**Interactions:**

**Dopamine-depleting agents:** Concomitant use with tetrabenazine or other drugs known to deplete monoamine stores is not recommended. **Antihypertensive agents:** Symptomatic postural hypotension. Dose adjustment of the antihypertensive agent may be required. **Antidepressants:** Hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants. **Anticholinergics:** may affect Sinemet's absorption. **Iron:** when ingested a decrease has been shown in the carbidopa and/or levodopa bioavailability.

**Other interactions:** Dopamine D2 receptor antagonists and isoniazid, may reduce the effects of levodopa. Effects reduced by phenytoin and papaverine. Patients should be carefully observed. Concomitant use with selegiline and may be associated with severe orthostatic hypotension. The absorption of Sinemet may be impaired in some patients on a high protein diet.

**Use in pregnancy and lactation:** Do not use during pregnancy or breast-feeding.

**SIDE EFFECTS**

Refer to SPC for complete information on side effects

Most frequently reported: dyskinesias including choreiform, dystonic and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction. Other adverse reactions: syncope, chest pain, anorexia, cardiac irregularities and/or palpitations, hypotensive episodes, hypertension, phlebitis, vomiting, gastro-intestinal bleeding, diarrhoea, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, angioedema, urticaria, pruritus, Henoch-Schonlein purpura, neuroleptic malignant syndrome, bradykinetic episodes, dizziness, paresthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with
or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion, increased libido, somnolence, sudden sleep onset episodes, dyspnoea, alopecia.

**Overdose:** treat as per acute levodopa overdose. ECG monitoring should be instituted.

**PACKAGE QUANTITIES AND BASIC NHS COST**
Sinemet 12.5 mg/50 mg Tablets – PVC/AL blister packs of 90 tablets £6.28
Sinemet 10 mg/100 mg Tablets – PVC/AL blister packs of 100 tablets £7.30
Sinemet Plus 25 mg/100 mg Tablets - PVC/AL blister packs of 100 tablets £12.88
Sinemet 25 mg /250 mg Tablets - PVC/AL blister packs of 100 tablets £18.29
Sinemet CR 50mg/200 mg Prolonged–Release Tablets - All aluminium blister packs of 60 tablets £11.60
Half Sinemet CR 25 mg/100 mg Prolonged-Release Tablets - All aluminium blister packs of 60 tablets £11.60

**Marketing Authorisation Numbers**
PL 00025/0226 Sinemet 12.5 mg/50 mg Tablets
PL 00025/0084 Sinemet 10 mg/100 mg Tablets
PL 00025/0150 Sinemet Plus 25 mg/100 mg Tablets
PL 00025/0085 Sinemet 25 mg /250 mg Tablets
PL 00025/0269 Sinemet CR 50mg/200 mg Prolonged–Release Tablets
PL 00025/0287 Half Sinemet CR 25 mg/100 mg Prolonged-Release Tablets

**Marketing Authorisation Holder**
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