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Madopar the original 4+1 combination in three dosage forms, 62.5, 125 and 250
'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.

Therefore 'Sinemet-Plus' is an effective low level introduction to levodopa therapy for:

☐ patients on anticholinergics requiring 'add on' levodopa therapy
☐ first-time patients requiring low levels of levodopa
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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:

- Sinemet25 containing 10 mg carbidopa and 100 mg levodopa.
- Sinemet100 containing 25 mg carbidopa and 100 mg levodopa.
- Sinemet275 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 that need a higher dosage should be switched to Sinemet/275. Dosage with either form should not exceed eight tablets a day. If patients do a 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 excessive dosage in some patients.

Sinemet100 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 1500 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
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 antipsychotic reactions. 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 brad dopamine following administration of levodopa, and use of Sinemet may cause a recurrence. It is concommitant administration of psychoactive 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 gastro-intestinal 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 Coombe 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 vascular 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. benztpine 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 may 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
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, salivation,
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 Horner'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' 257 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' 257 Tablets (100) £12.20.
'Sinemet-Plus' Tablets (100) £10.70.
'Sinemet' 110 Tablets (100) £6.30.

Product licence numbers:
'Sinemet' 257 Tablets, 0025/0069.
'Sinemet-Plus' Tablets, 0025/0150.
'Sinemet' 110 Tablets, 0025/0084.

Product authorisation numbers:
'Sinemet' 257 Tablets, 35/47/2.
'Sinemet-Plus' Tablets, 35/47/3.
'Sinemet' 110 Tablets, 35/47/1.

Agents in the Republic of Ireland:
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Additional information is available to the medical profession
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Epilim is a powerful anticonvulsant capable of providing control for the majority of adults with tonic-clonic seizures or other epilepsies, including those not well controlled on previous treatments. Because it controls without sedation, Epilim allows many patients to lead full, normal lives.

Presentation
2. Epilim tablets: A white scored tablet containing 200mg sodium valproate.
4. Epilim Syrup: A red cherry-flavoured syrup containing 200mg sodium valproate per 5mL.

Indications
- Epilepsy in patients of all ages. Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and Administration
- To be taken with or after food: enteric-coated and plain tablets should be swallowed whole. Omit routine dosage should be established using the 200mg enteric-coated tablet. Epilim 500 enteric-coated is recommended for patients requiring high dosages.

Adults: Dosage should start at 600mg/day in divided doses, increasing by 200mg/day at three-day intervals until control is achieved. (Maximum Dose 2400mg/day).

In patients already receiving another therapy the same pattern should be followed. Dosage of barbiturates should be reduced as that of Epilim is increased; the respective dosages should be adjusted, preferably during the stabilisation period, to give optimum control at the lowest possible combined-dose level, and it may be possible to maintain control with Epilim alone.

Once known enzyme-inhibitors have been withdrawn, it may be possible to maintain secure control with a reduced dose of Epilim. Although a method of measuring plasma levels is available, optimum dosage must ultimately be determined by seizure-control (Children under 10y: Initially 400mg/day in divided doses with spaced increases until control is achieved (usually in the range of 20-30mg/kg/day). Children under 20y: 20mg/kg of body weight per day; in severe cases, this may be increased up to 50mg/kg/day but should be undertaken only in patients in whom plasma valproate levels, clinical chemistry and haematological parameters can be monitored.

Contra-Indications, Warnings, etc.
Liver dysfunction, including hepatitis failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. The incidence of hepatic failure appears to be low, occurring during the first six months of therapy. The period of maximum risk being 2-12 weeks. No deaths have occurred in patients receiving the drug continuously for more than 6 months.

Biochemical tests may not always become abnormal early in the evolution of hepatic failure. Non-specific findings such as loss of serum control, malaise, anorexia and vomiting, developing after a period of satisfactory Epilim treatment may alert the clinician to the possibility of hepatic damage.

Epilim should not be administered to patients with pre-existing hepatic dysfunction. All patients for whom treatment with Epilim is contemplated should have baseline liver function tests (including serum fibrinogen and albumin levels) prior to commencement of therapy. Liver function should be carefully monitored, particularly during the first 6 months of therapy, and when dosage is being titrated upwards. Patients with a prior history of liver disease or with severe or unusual medical disorders, e.g. those accompanied by mental retardation or organic brain disease, should be followed particularly carefully. Transient elevations of liver enzymes are not uncommon during early treatment with Epilim, but if elevations are accompanied by other evidence of hepatic dysfunction, especially raised serum bilirubin or lowered serum fibrinogen, then the drug should be immediately withdrawn.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This may manifest clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, Epilim should be discontinued.

Valproate can inhibit second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Patients receiving Epilim should be monitored for platelet function before major surgery. Red cell hypoplasia and leukopaenia have been reported. The blood picture returned to normal when the drug was discontinued. Pancreatitis has occurred in patients receiving valproic acid or sodium valproate. Patients experiencing acute abdominal pain should have serum amylase estimated.

Minor gastric irritation and, less frequently, nausea may occur at the start of treatment but these problems can usually be overcome by administering Epilim tablets or syrup with or after food, or by transferring the patient to the Epilim enteric-coated formulations. Transient hair loss has been noted in some patients. Regrowth normally begins within six months. Oedema has been reported. Increase in alertness, appetite and weight may occur. Combined medication: Epilim is generally well tolerated in combination with other anti-epileptic agents. However, as interaction occurs between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anti-convulsant therapy. Epilim may also potentiate the effect of monoamine oxidase inhibitors and other anti-depressants, and dosage of such compounds should be reduced.

Diabetic patients: Epilim may give false positives in urine testing for ketones. Care should be taken when treating diabetic patients with Epilim Syrup which contains 3.4g sucrose per 5mL.

Women of childbearing age: Valproic acid or sodium valproate, like certain other anti-convulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.

Further Information
- When plasma valproic acid is within the recommended range of 50-120mg/litre (350-840nmol/litre) and serum albumin levels are normal, about 90% of the drug is bound to albumin. If the total plasma valproic acid concentration is below the upper range of normal, or if there is hypalbuminaemia, the percentage of free valproic acid may rise markedly in proportion to any dosage increase and may be associated with a higher incidence of adverse effects.

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- Epilim Tablets 0623/0007
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