Presentation
Madopar contains a combination of levodopa and the decarboxylase
inhibitor benserazide in the ratio of
1:1 Madopar 62.5 capsules
containing 50mg levodopa and
12.5mg benserazide hydrochloride
(equivalent to 12.5mg of the base)
Madopar 125 capsules containing
100mg levodopa and 25mg
benserazide hydrochloride
(equivalent to 25mg of the base)
Madopar 250 capsules containing
200mg levodopa and 50mg
benserazide hydrochloride
(equivalent to 50mg of the base)

Indications
Parkinsonism—idiopathic, post-
cephalitic

Dosage
Dosage is variable and the data sheet should be consulted for full
details. The effective daily dose
usually varies between four and eight
capsules of Madopar 125 (two to
four capsules of Madopar 250) daily
in divided doses. Most patients
require more than six capsules
of Madopar 125 daily. In some
elderly patients, initial treatment with
one capsule of Madopar 62.5 once
or twice daily, increasing by one
capsule every third or fourth day
may suffice. Patients who
experience fluctuations in response
may also benefit from administration
of smaller more frequent doses
using Madopar 62.5

Contra-indications
Narrow-angle glaucoma, severe
psychoneuroses or psychoses. It
should not be given in conjunction
with monoamine oxidase inhibitors
or within two weeks of their
withdrawal, to patients under
25 years of age, to pregnant women
or to patients who have a history of,
or who may be suffering from, a
malignant melanoma

Precautions
Drugs which interfere with central
amine mechanisms should be
avoided. Endocrine, renal,
pulmonary or cardiovascular
disease; hepatic disorder; peptic
ulcer, osteoporosis, sympathectomy.
drugs, antihypertensive drugs. Patients
who improve on Madopar therapy
should be advised to resume normal
activities gradually as rapid
mobilisation may increase the risk of
injury

Side-effects
Nausea and vomiting,
cardiovascular disturbances,
psychiatric disturbances,
involuntary movements

Packings
Madopar 62.5 capsules, Madopar
125 capsules and Madopar 250
capsules in packings of 100

License Numbers
0031/0125 (Madopar 62.5
capsules), 0031/0073 (Madopar 125
capsules), 0031/0074 (Madopar 250
capsules)

Basic NHS Cost
Madopar capsules 62.5
£4.01 per 100
Madopar capsules 125
£7.23 per 100
Madopar capsules 250
£12.94 per 100

Roche
Roche Products Limited
PO Box 8
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Hertfordshire AL7 3AY

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the original 4+1 combination
in three dosage forms, 62.5, 125 and 250
SINEM
Carbidopa and levodopa, MSD
A NEW START
'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
- patients with a low levodopa tolerance to allow relatively higher levels of carbidopa

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.
PRESCRIBING INFORMATION

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® containing 10 mg carbipoda and 100 mg levodopa.
- Sinemet-Plus® containing 25 mg carbipoda and 100 mg levodopa.
- Sinemet® 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.

Patients who require less than 700 mg levodopa given as 'Sinemet®' or 'Sinemet®' 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®' 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®'. 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 tremor, may be helpful.

Patients 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-Plus' should be substituted three or four times a day. If further titration is necessary, the dosage of 'Sinemet®' 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®' 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 monamine 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 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 unusual or unpredictable 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 barbiturates 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 phenothiazin and piperazine 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 intraocular 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 asymptomatic postural hypotension has 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.

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 vaginal 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, benztropine mesylate, 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
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, 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 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' is 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) £12.50
'Sinemet-Plus' Tablets (100) £10.70
'Sinemet 110' Tablets (100) £5.50

Product licence number:

'Sinemet 257' Tablets, 0025/0085.
'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:

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

Additional information is available to the medical profession on request.

Issued September 1981.

® denotes registered trademark. TM denotes trademark.

Merck Sharp & Dohme Limited, Hoddesdon, Hertfordshire, EN11 9BU
882.SEM.81.GB.7952.1
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
1. Epilim 200 enteric-coated: A lilac-coloured enteric-coated tablet containing 200mg sodium valproate
2. Epilim tablets: White scored tablet containing 500mg sodium valproate
3. Epilim 500 enteric-coated: A lilac-coloured enteric-coated tablet containing 500mg sodium valproate
4. Epilim Syrup: A red cherry-flavoured syrup containing 200mg sodium valproate per 5ml

Indications
Epilepsy: In women of childbearing age, 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. Optimum 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 6000mg/day.)

In patients already receiving other therapy, the same pattern should be followed.

Dose adjustment in patients receiving other therapies may be required. If Epilim is increased, the respective dosages should be increased during the stabilisation period to give optimum control at the lowest possible combined-dose level, and it may be found possible to maintain control with Epilim alone.

Once known enzyme-inducers have been withdrawn, it may be possible to maintain seizure control at a reduced dose of Epilim. Although a method of measuring plasma levels is available, optimum dosage must usually be determined by seizure control. Children over 2kg: Initial 400mg/day in divided doses with increased dosages until control is achieved usually in the range of 20-30mg/kg/day.

Children under 2kg: 200mg/kg of body weight per day, in divided doses, until control is achieved. This may be increased up to 50mg/kg/day but should be undertaken only in patients in whom plasma valproate levels, clinical chemistry and hematological parameters can be monitored.

Contra-Indications, Warnings, etc.
Lever dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. The incidence of fatalities occurred 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. No specific findings such as loss of seizure 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 base line lever function assessed including serum fibrinogen and albumin levels prior to commencement of therapy. Lever function should be carefully monitored, particularly during the first six months of therapy, and when dosage is being titrated upwards.

Patients with a prior history of liver disease, or with severe or unusual lever 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 may 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.

Valproic acid inhibits 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 leukopenia have been reported. The blood picture returned to normal when the drug was discontinued. Pericarditis has occurred in patients receiving valproic acid or sodium valproate.

Women or 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 50-1200mg/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 rises above the upper range of normal, or if there is hypoalbuminaemia, 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.

Product Licence Numbers, Names and Addresses
Epilim 200 enteric-coated tablets 0623/0006
Epilim tablets 0623/0001
Epilim 500 enteric-coated tablets 0623/0005
Epilim Syrup 0623/0004

NHS Cost
Epilim 200 enteric-coated tablets 100: £7.44
Epilim 500 enteric-coated tablets 100: £7.80
Epilim Syrup 200ml: £4.03
Epilim 200mg tablets 100: £5.45

LABAZ: Sanofi UK Ltd
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Additional information is available from the Company.
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sodium valproate

200 enteric-coated, 500 enteric-coated tablets; syrup.
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