Depression...disturbed sleep...

Sinequan
brand of doxepin
Trade Mark

lifts depression...
promotes restful sleep

■ SEDATIVE ANTIDEPRESSANT
■ ONCE NIGHTLY DOSAGE

Indications: depression with or without anxiety. Contraindications: glaucoma, urinary retention, hypersensitivity to the drug. Side effects: dry mouth and drowsiness are most commonly reported. Precautions: Sinequan may potentiate other compounds - e.g. monoamine oxidase inhibitors; not recommended in pregnancy or children under 12 years of age. Dosage: range 30 mg to 200 mg daily in divided doses, up to 100 mg may be given as a single dose at night. Packs and Basic N.H.S. Cost:
10 mg capsules (PL 57/5032), pack of 100, £2.98; 25 mg capsules (PL 57/5033), pack of 100, £4.24; 50 mg capsules (PL 57/5034) pack of 100, £7.01; 75 mg capsules (PL 57/0133), pack of 60, £6.64.

Full information on request to the Company.

Pfizer
PFIZER LIMITED
SANDWICH, KENT.
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.

DOSE AND ADMINISTRATION
The optimal daily dosage of 'Sinemet' must be determined by careful titration for each patient.
'Sinemet' Tablets are available as:
- 'Sinemet' 100 containing 10 mg carbidopa and 100 mg levodopa.
- 'Sinemet-Plus' containing 25 mg carbidopa and 100 mg levodopa.
- 'Sinemet-250' 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' 250 will 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' 250 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-250'. Dopamine with either form should not exceed eight tablets a day. If patients do not 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' 100 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-250' should be substituted three or four times a day. If further titration is necessary, the dosage of 'Sinemet-250' may be increased gradually to a maximum of eight tablets a day.

Patients receiving levodopa: Discontinue levodopa at least two 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-250' 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 decreased by at least 50% 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.

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 anticholinergic 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 brad 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 intraocular 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 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. 'Sinemet' 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, SOFT, 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. benztrazepine meperidine, benzenzhydrochloride, 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 rigidity and akinesia 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, tinnitus, urological crisis, weakness, numbness, bruxism.

Gastro-intestinal: constipation, diarrhoea, epigastric and abdominal distress and pain, flatulence, hiccup, 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 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) £12.20
'Sinemet-Plus Tablets (100) £10.70
'Sinemet' 110 Tablets (100) £6.30.

Product licence numbers:

'Sinemet' 257 Tablets 0025/0085
'Sinemet-Plus Tablets 0025/0050
'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.

™ denotes trademark.

Price: Inland £4.50

Abroad US $20.50 including postage

(Concessionary price to BMA Members: Inland £4.00; Abroad US $19.00. When ordering BMA Members must quote their membership number or the full price will be applicable.)

*Including airmail postage.

Payment must be enclosed with order or surcharge of 50p will be made for rendering invoices and statements

Order your copy now from

The Publisher,

BRITISH MEDICAL JOURNAL,

BMA House,

Tavistock Square,

London WC1H 9JR

or through any leading bookseller.
the right balance in Parkinson's disease

Madopar
levodopa plus benserazide
the original 4+1 combination in three dosage forms 625 125 and 250
Disipal has made her a little more responsive to her phenothiazine therapy.

The addition of Disipal to phenothiazine therapy enables optimum therapeutic response to be achieved without unacceptable side effects. Disipal also elevates the patient's mood, thus relieving the depression so often associated with major tranquilizer therapy.

Drug of choice
Following a three month double blind crossover trial, the authors concluded that "orphenadrine is the drug of choice in the treatment of drug induced extrapyramidal reactions and depression."

Increased response
Furthermore, the authors postulate that "the introduction of orphenadrine in the treatment of a patient whose response to phenothiazines is not maintained, might well result in further benefit."

For patients on major tranquilizer therapy

Disipal

* controls extra-pyramidal reactions
* elevates patient mood.

For more information, contact your physician or pharmacist.

Full prescribing information on request.

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

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 lac-coloured enteric-coated tablet containing 200mg sodium valproate
2. Epilim tablets: A white scored tablet containing 200mg sodium valproate
3. Epilim 500 enteric-coated: A lac-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 not responding 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: 2600mg/day). In patients already receiving other therapy, the same pattern should be followed. Dosage of narcotics should be reduced as that of Epilim is increased. The respective dosages should be adjusted during the stabilisation period. The optimum dosage must be determined by the severity of the patient's condition. It may be possible to maintain control with Epilim alone.

Children under 10kg: Initially 200mg/day in divided doses with a further increase until control is achieved (usually in the range of 20-30mg/kg/day). Children under 20kg: 20mg/kg of body weight per day, in several cases, this may be increased up to 60mg/kg/day but should be undertaken only in patients who respond. Dosage levels are now adjusted in body-weight to the lowest possible combined dosage level. It may be possible to maintain control with Epilim alone.

Contra-Indications, Warnings, etc.
Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents 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. Non-specific findings such as loss of liver function, jaundice, anaemia and vomiting, developing after a period of exacerbation of the liver damage, should be carefully considered. Particular concern should be given to patients with a prior history of liver disease or with severe or unexplained liver function disorders, e.g. those accompanied by mental retardation and/or organic brain disease. It should be noted that in a patient with a prior history of liver disease, the liver function will be affected more severely than in a patient without such a history. Transient elevations in liver enzymes are not uncommon during early treatment with Epilim. However, an elevation that is not accompanied by other evidence of hepatic dysfunction, especially raised serum bilirubin or lowered serum alkaline phosphatase, should be investigated further.

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

Valproic acid exerts a second stage of sedative action. Minor sedation, such as drowsiness and feeling of well-being, have been reported in patients receiving Epilim. Patients must be warned that they may feel drowsy. If this is of concern, the dose of Epilim should be reduced. The drug may be continued for a while in the absence of drowsiness, if necessary due to the risk of a reduction in the dose of Epilim may be necessary.

Menstrual withdrawal bleeding and/or breakthrough bleeding have been reported. If the drug is stopped, the withdrawal bleeding may be heavy and prolonged. If breakthrough bleeding occurs, the dose of the drug should be increased.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients treated with valproic acid or sodium valproate. Patients treated with Epilim should be monitored for lactic acidosis. If lactic acidosis is suspected, Epilim should be discontinued.

Further Information
When plasma valproic acid is within the recommended range of 60-210mg/l, patients have no side effects. If the total plasma valproic acid is above the upper range of normal, or if there is hyperammonaemia, the combination of these effects may lead to a reduction in the dosage. Additional information is available from the Company.
For many grand mal patients

a full, normal life under the protection of

Epilim
sodium valproate

200 enteric-coated, 500 enteric-coated tablets, syrup
The New MS8.

Like the MS6, but allows you to spend more time being a doctor.

Medelec Limited, Manor Way, Old Woking, Surrey GU22 9JU
Telephone: Woking: 04862 7054
Telex: 859141 Medelec G
Micra-fine
A New Range of Fine Microsurgical Titanium Instruments specifically designed for a wide range of procedures including micro-anastomosis

Developed jointly by Downs Surgical and Micra from the original Microsurgical Instruments designed by Dermot Pierse
This new range of instruments is ideally suited to all types of microsurgery and especially suitable for the anastomosis of very small vessels. Therefore there are applications in Microvascular Surgery, Plastic Surgery (e.g. replanting digits), Gynaecology (e.g. repair of fallopian tubes), Urology (e.g. reversal of vasectomy), Neurosurgery, Orthopaedic Surgery, Hand Surgery and all other fine surgical procedures performed under the microscope, with telescopic loupes or with simple binocular loupes.

Manufactured in Titanium
The particular metallurgical properties of titanium make it the ideal material for fine surgical instruments. Titanium instruments are non-magnetic, lighter weight, have greater strength and are longer lasting than conventional stainless steel micro surgical instruments. The blue titanium oxide finish minimises the light reflection under the microscope.

Downs Surgical

To: Downs Surgical Ltd., Church Path, Mitcham, Surrey CR4 3UE, England. Please send me details of Micrafine Microsurgical Titanium Instruments.

Name ____________________________
Address __________________________
STATISTICS AT SQUARE ONE

from the British Medical Journal

The statistical testing of data is indispensable in many types of medical investigation and a help on countless occasions in clinical practice. This book provides step-by-step instruction. Subjects covered include standard deviation, $\chi^2$ tests, t tests, non-parametric tests, and correlation. The book includes sections on Fisher's exact probability test and rank correlation not published in the B.M.J. series. Methods specially adapted to pocket calculators.

"The ability to put symbols in sequence may well be one of the greatest advances in man's development... This excellent and attractive volume will give you an idea into which category an article or projected article fits. The ink you save may be your own. It is superb value."

"... this gem of a practical booklet squeezes the essence of biostatistics into 75 well-written, well-organized pages. Newcomers to the field will like the way obscure concepts are clarified; experts will find the book valuable as a teaching aid."

Seventh edition

Now available

PRICE: Inland £2.50
Overseas US$10.00,
including postage by air mail

Payment must be enclosed with order or a surcharge of 50p will be made for rendering invoices and statements

ORDER YOUR COPY NOW
From: The Publisher,
British Medical Journal,
BMA House,
Tavistock Square,
London WC1H 9JR
or through any leading bookseller

Published by British Medical Association, Tavistock Square, London WC1H 9JR
and printed in England by Eyre & Spottiswoode Ltd, Thanet Press, Margate, Kent