SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Madopar® Tablets

COMPOSITION

Each Madopar 250 mg tablet (cross-scored tablet) contains 200 mg levodopa and 50 mg benserazide (as the hydrochloride).

Excipients: calcium hydrogen phosphate, colloidal anhydrous silica, crospovidone, docusate sodium, ethylcellulose, iron oxide red (E172), magnesium stearate, mannitol, microcrystalline cellulose, pregelatinised maize starch.

PHARMACOLOGICAL CLASSIFICATION

A 5.4.1 Anti-Parkinsonism preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Parkinson's disease:

Dopamine, which acts as a neurotransmitter in the brain, is not present in sufficient quantities in the basal ganglia of Parkinsonian patients. Levodopa (INN) or L-DOPA (3,4-dihydroxy L-phenylalanine) is an intermediate in dopamine biosynthesis. Levodopa (dopamine precursor) is used as a prodrug to increase dopamine levels since it is able to cross the blood-brain barrier whereas dopamine itself cannot. Once levodopa has entered the central nervous system (CNS), it is metabolised to dopamine by aromatic L-amino acid decarboxylase

Replacement therapy is performed by administering levodopa, the immediate metabolic precursor of dopamine, since the latter substance has only a very limited ability to cross the blood-brain barrier.

After administration, levodopa is rapidly decarboxylated to dopamine in the extracerebral as well as cerebral tissues. This concurrent administration of levodopa and benserazide, a peripheral decarboxylase inhibitor, inhibits the peripheral (extracerebral) metabolism of levodopa. Madopar is a combination of these two substances in the proportion 4:1.

Pharmacokinetic properties

Absorption: Levodopa and benserazide are for the most part (66 - 74 %) absorbed in the upper regions of the small intestine. The maximum plasma concentration of levodopa is reached approximately one hour after ingestion of Madopar. The bioavailability of levodopa from Madopar is 98 % (range 74 -112 %). Food intake reduces the rate of levodopa absorption. The peak levodopa plasma concentration is 30 % lower and occurs later when Madopar tablets are administered after a standard meal. The extent of levodopa absorption is reduced by 15 % due to an increase in gastric emptying time.

Distribution: Levodopa crosses the blood-brain barrier by a saturable transport system. It is not bound to plasma proteins, and its volume of distribution is 57 litres. The AUC of levodopa in cerebrospinal fluid is 12 % of that in plasma.

In contrast to levodopa, benserazide does not penetrate the blood-brain barrier at therapeutic doses. It is concentrated mainly in the kidneys, lungs, small intestines and liver.

Metabolism: Levodopa is metabolised by two major pathways (decarboxylation and O-methylation) and two minor ones (transamination and oxidation). Aromatic amino acid decarboxylase converts levodopa to dopamine. The major end products of this pathway are homovanillic acid and dihydroxyphenylacetic acid.

Catechol-O-methyltransferase methylates levodopa to 3-O-methyldopa. This major plasma metabolite has an elimination half-life of 15 - 17 hours, and it accumulates in patients who receive therapeutic doses of levodopa. Decreased peripheral decarboxylation of levodopa, when it is administered with benserazide, is reflected in higher plasma levels of levodopa and 3-O-methyldopa and lower plasma levels of catecholamines (dopamine, noradrenaline) and phenolcarboxylic acids (homovanillic acids, dihyroxyphenylacetic acid).

Benserazide is hydroxylated to trihydroxybenzylhydrazine in the intestinal mucosa and the liver. This metabolite is a potent inhibitor of the aromatic amino acid decarboxylase.

Elimination: In the presence of peripherally inhibited levodopa decarboxylase, the elimination half-life of levodopa is approximately 1,5 hours. The elimination half-life is slightly longer (25 %) in elderly patients with Parkinson's disease. The clearance of levodopa from plasma is about 430 mℓ/min.

Urinary recovery of levodopa is about 7 % of a dose. Levodopa is eliminated by biotransformation and excretion of the metabolites in the urine.

Benserazide is almost entirely eliminated by metabolism. The metabolites are mainly excreted in the urine and to a smaller extent in faeces.

INDICATIONS

Parkinsonism of the idiopathic and symptomatic varieties, but excluding drug-induced Parkinsonism.

CONTRAINDICATIONS

Madopar is contraindicated in patients with a known hypersensitivity to levodopa or benserazide or to any of the ingredients contained in Madopar.

Madopar must not be given in conjunction with monoamine oxidase (MAO) inhibitors. The same contraindications apply as for sympathomimetic agents (such as epinephrine (adrenaline) and norepinephrine (noradrenaline) and their derivatives). Madopar must not be given to patients with decompensated endocrine, renal or hepatic function, cardiac disorders, glaucoma, psychoses and highly pronounced psychoneuroses. Madopar must not be administered to patients under 25 years of age (skeletal development must be complete prior to Madopar administration).

Pregnancy and Lactation (see PREGNANCY AND LACTATION).

WARNINGS and SPECIAL PRECAUTIONS

Neuroleptic malignant syndrome: Madopar must not be withdrawn abruptly. Abrupt withdrawal of the preparation may result in neuroleptic malignant-like syndrome (hyperpyrexia and muscular rigidity, possible psychological changes and elevated serum creatinine phosphokinase) which may be life-threatening. Should a combination of such symptoms and signs occur, the patient should be kept under medical surveillance, if necessary, hospitalised and rapid and appropriate symptomatic treatment given. This may include resumption of Madopar therapy after an appropriate evaluation.

SPECIAL PRECAUTIONS

Hypersensitivity reactions may occur in susceptible individuals. All patients should be carefully observed for signs of depression with suicidal tendencies or other serious behavioural changes. Extreme caution should be used in treating patients with a history of psychotic disorders or who are receiving psychotherapeutic agents such as phenothiazines or tricyclic anti-depressants. Care should be exercised in administering Madopar to patients with a history of myocardial infarction or who have atrial, nodal or ventricular arrhythmias. Patients with cardiac abnormalities should have

their treatment with Madopar initiated in a facility with adequate monitoring equipment and provision for intensive care.

General: Regular assessment of cardiovascular, hepatic, haematopoietic and renal function should be performed in all patients during extended therapy.

Patients treated with Madopar may not take MAO inhibitors.

When combined with sympathomimetics, the latter may have a stronger effect. It is necessary, therefore, to monitor the cardiovascular functions and if necessary, the dose of the sympathomimetic should be reduced.

The taking of other anti-Parkinsonism medicines must not be stopped suddenly when treatment with Madopar is commenced, as there is often a long latent period before Madopar takes effect. In certain cases the dose of other anti-Parkinsonism medicines can gradually be reduced at a later stage.

Use in patients with glaucoma: Regular measurement of intra-ocular pressure is advisable in patients with open-angle glaucoma, as levodopa such as contained in Madopar, has the potential to raise intra-ocular pressure.

Patients with chronic wide-angle glaucoma can be treated cautiously with Madopar, provided the intra-ocular pressure is well controlled and monitored carefully during therapy. Rarely pupillary dilatation and activation of latent Horner's syndrome have been reported during levodopa treatment.

Diabetes: Patients with diabetes should undergo frequent blood sugar tests, and the dosage of anti-diabetic agents should be adjusted to blood sugar levels.

Patients who have a past history of myocardial infarction, coronary insufficiency or cardiac dysrrhythmia must be subjected to periodical cardiovascular check-ups, by means of ECG.

Patients with a history of convulsive disorders should be treated cautiously if Madopar is incorporated into their regimen.

The possibility of upper gastro-intestinal haemorrhage occurring in patients with a history of peptic ulcer must be borne in mind when treating them with Madopar.

Use in patients with osteoporosis and osteomalacia: The effects of Madopar on human bone during prolonged administration is not known. It should be remembered that elderly people have a high incidence of subclinical osteoporosis and osteomalacia.

A combination with anti-hypertensive medicines is possible, provided that the blood pressure of the patient is taken regularly (possibility of an additional effect).

Physical Activity: Patients with severe parkinsonism who improve on Madopar therapy should be advised to resume normal activities gradually and with caution as rapid mobilisation may increase the risk of injury.

Psychoactive medicines: If concomitant administration of psychoactive medicines are necessary, they should be administered with great caution. Patients should be carefully observed for unusual, untoward medicine effect (see "CONTRAINDICATIONS" and "WARNINGS AND SPECIAL PRECAUTIONS"). Phenothiazines and butyrophenone derivatives may antagonise Madopar and should not be used, in combination with Madopar.

Anaesthesia: If a patient on Madopar requires a general anaesthetic, the normal Madopar regimen should be continued as close to the surgery as possible, except in the case of halothane. In general, for anaesthesia with halothane, Madopar should, be withdrawn 12 - 48 hours before surgical intervention, as fluctuations in blood pressure and/or dysrrhythmias may occur in patients on Madopar therapy. Subsequently, the treatment is resumed, slowly increasing the dose, until the pre-operative dose-level is reached.

In surgical emergencies, when Madopar has not been withdrawn, halothane must be avoided in anaesthesia. During the operation the patient must be monitored very closely.

Somnolence: Madopar has been associated with somnolence and episodes of sudden sleep onset. 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 Madopar (see also Effects on the ability to drive and use machinery). A reduction of dosage or termination of therapy may be considered.

Dopaminergic medicines: Compulsive behaviour such as gambling, hypersexuality, shopping, eating, medication use and punding (repetitive purposeless activity) has been reported in patients taking dopamine agonists for Parkinson's Disease, especially at high doses. There is no established causal relationship between benserazide, which is not a dopamine agonist, and these events. However, caution is advised as levodopa is a dopaminergic medicine. Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences.

Effects on ability to drive and use machines

Patients being treated with Madopar and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved.

Potential for Drug Dependence or Abuse

A sub-group of Parkinson's disease patients have been shown to suffer from cognitive and behavioural disturbances that can be directly attributed to taking increasing quantities of medication against medical advice and well beyond the doses required to treat their motor disabilities.

INTERACTIONS

Co-administration of the anti-cholinergic medicine trihexyphenidyl with Madopar tablets reduces the rate, but not the extent, of levodopa absorption.

Ferrous sulphate decreases the maximum plasma concentration and the AUC of levodopa by 30 - 50 %. The pharmacokinetic changes observed during co-treatment with ferrous sulphate appear to be clinically significant in some but not all patients.

Metoclopramide increases the rate of levodopa absorption.

Domperidone may increase the bioavailability of levodopa by stimulation of gastric emptying.

Cardiovascular medicines: Postural hypotensive episodes have been reported; therefore, Madopar should be administered cautiously and blood pressure monitored in patients on antihypertensive medication. Furthermore, special care is required with alpha methyldopa which is a substrate for the enzyme dopa decarboxylase.

The action of Madopar is inhibited by neuroleptics and opioids.

Madopar should not be administered concomitantly with MAO inhibitors, there should be an interval of at least two weeks between stopping the MAO inhibitor and starting Madopar therapy.

Madopar should not be administered concomitantly with sympathomimetic agents (adrenaline, noradrenaline, isoprenaline or dexamphetamine) as their effect may be potentiated by levodopa. If concomitant administration should be necessary, monitoring of the cardiovascular system is essential, and the dose of the sympathomimetic agent may need to be reduced.

The effect of Madopar is not impaired by multivitamin preparations containing vitamin B6.

Combination with other anti-parkinsonian agents (anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists) is permissible, though such combination may intensify both the desired and the undesired effects.

Dosage adjustment of Madopar or the other substance may be required. When initiating adjuvant treatment with a COMT inhibitor, a reduction of the dosage of Madopar may be necessary. Anticholinergics should not be withdrawn abruptly if therapy with Madopar is instituted.

Absorption of levodopa from the gastrointestinal tract is impaired when Madopar is taken with a protein-rich meal.

Concomitant administration of antipsychotics with dopamine-receptor blocking properties, particularly D2-receptor antagonists might antagonise the antiparkinsonian effects of levodopa-benserazide. Levodopa may reduce antipsychotic effects of these medicines. These medicines should be co-administered with caution.

Interference with Laboratory Tests

Madopar therapy may increase urinary catecholamines and metabolites and may therefore interfere with interpretation of urinary assays, e.g. diagnosis of adrenal tumours.

Coombs' test may give false positive results in patients on Madopar therapy.

"T" wave increase was observed in 27 % of patients in one study. "PR" intervals may increase.

Uric acid, creatinine, and glucose estimation may be interfered with by levodopa. For reported biochemical disturbances see "SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS – Investigations".

PREGNANCY AND LACTATION

Madopar is absolutely contraindicated in pregnancy and in women of childbearing potential in the absence of adequate contraception, because of the possibility of disturbed foetal skull development. Should a woman who is being treated with Madopar become pregnant, the treatment must be discontinued (as advised by the prescribing medical practitioner. Since it is not known whether benserazide passes into breast milk, mothers requiring Madopar treatment should not breastfeed their infants, since the occurrence of skeletal malformations in the infants cannot be excluded.

DOSAGE AND DIRECTIONS FOR USE

Method of administration: Madopar tablets may be broken into small pieces to facilitate swallowing. Since absorption may be impaired by food intake (see PHARMACOLOGICAL ACTION

- Pharmacokinetics), Madopar should be taken at least 30 minutes before, or 1 hour after meals whenever possible. If undesirable gastrointestinal effects occur, they can be controlled by taking Madopar with some food or liquid.

Standard dosage: Treatment with Madopar should be introduced gradually; dosage should be assessed individually and titrated for optimal effect. The following dosage instructions should therefore be regarded as guidelines.

Initial therapy: The initial dosage recommended is ½ tablet three times daily. The daily dosage should then be increased by ½ tablet at weekly intervals until the individual therapeutic dosage is reached. If the patient can be examined regularly, the dosage may be increased more rapidly e.g. the daily dosage can be increased by ½ tablet twice a week. Thus an effective dosage may be reached. The effective dosage is generally between 2 and 4 tablets daily, divided into three or four doses. It is rarely necessary to administer more than 5 tablets daily.

Example:

Number of Tablets of Madopar 250 mg					
	Morning	**Noon**	**4 p.m.**	**Evening**	**Total number per day**
Week 1	½	½		½	1½
Week 2	½	½	½	½	2
Week 3	1	½	½	½	2½
Weeks 4 & 5	1	1	½	½	3
If improvement is not satisfactory, increase dosage, but more slowly:					
Weeks 6 & 7	1	1	1	½	3½
Weeks 8 & 9	1	1	1	1	4

If it proves necessary to give more than 4 tablets, the dosage should be increased at monthly intervals.

If unacceptable side-effects occur during the initial stage of treatment, the dosage should not be increased further or should even be reduced. Interruption of treatment is seldom necessary.

When the side-effects disappear or become tolerable the daily dosage should be increased again but more slowly, e.g. by a ½ tablet every two or three weeks only.

The recommended interval between dosage increases is longer when the average effective dosage (3 tablets daily) is exceeded, since it may take some time for the full therapeutic effect of Madopar to develop. Therapy with Madopar should be continued for at least six months before it is presumed to be ineffective.

Maintenance therapy: It is essential in all cases to divide the daily dosage into at least three doses. The average maintenance dosage is 1 tablet three times daily. However, since the improvement may fluctuate, division of the daily dosage (regarding both the number of individual doses and their distribution throughout the day) must be adapted to individual requirements.

Patients who experience large fluctuations in the effect of Madopar tablets during the course of the day (on-off phenomena) should receive smaller, more frequent single doses, be switched to controlled release formulations, or use alternative medication.

Changing from levodopa (L-dopa) to Madopar: Where it proves judicious to give Madopar to patients who have, up till then, been treated with levodopa, the changeover can be effected from one day to the next as follows: the number of Madopar tablets to be taken daily, is equal to half a tablet less than half the total number of 500 mg tablets or capsules of levodopa taken daily up to then. If, for instance, the patient has been taking 2 g levodopa (four 500 mg tablets daily), he should be prescribed 2 minus ½ = 1½ tablets of Madopar daily.

A minimum initial dosage of a ½ tablet of Madopar three times daily may be given in all cases. The patient should be observed closely for one week and then, if necessary, the dosage of Madopar

should be increased until a satisfactory improvement is obtained (the dosage is identical to that for patients not previously treated with levodopa). If deterioration in the patient's clinical condition is observed the dosage may be increased earlier. Patients already on levodopa therapy should be informed that their condition may deteriorate initially until the optimal dosage regimen has been found. Close medical supervision of the patient is advisable during the initial period while adjusting the dose.

Special dosage instructions: Dosage must be carefully titrated in the elderly. Patients on other anti-Parkinsonian agents may receive Madopar. However, as treatment with Madopar proceeds and the therapeutic effect becomes apparent, the dosage of the other medicines may need to be reduced or these medicines gradually withdrawn.

Over-responsiveness to Madopar (dyskinesia) may be controlled by increasing the length of the intervals between administrations rather than by reducing the single doses.

SIDE EFFECTS

Serious or life threatening reactions: The most common serious adverse reactions are due to central neuropharmacologic activity of Madopar, and can usually be diminished by dosage reduction. These include abnormal involuntary movements, dyskinesia, hyperkinesia and involuntary jerks, (muscle twitch and blepharospasm may be taken as early signs to consider dosage reduction). Other serious reactions are mental changes, including paranoid ideation and psychotic episodes; depression with or without suicidal tendencies, mania and hallucinations. Cardio-arrhythmias, angina pectoris and orthostatic hypotension have also been reported.

With prolonged treatment, fluctuations in therapeutic response may also be encountered. They include freezing episodes, end of dose deterioration and the “on-off” effect.

The more frequently reported adverse reactions associated with the use of Madopar are listed below. The events listed below are classified by body system:

Gastrointestinal disorders: Nausea and vomiting (although these occur significantly less often with Madopar than with levodopa alone), anorexia, constipation.

Body as a whole: weight gain, oedema, lassitude.

Central and peripheral nervous system disorders: dyskinesia, hyperkinesia, involuntary jerks (lips, head, tongue, cheeks, extremities), hiccups, insomnia, depression, nocturnal excitation, diurnal excitation, somnolence, dizziness, abnormal involuntary movements (eg. choreiform or athetotic) particularly at later stages of treatment.

Heart rate and rhythm disorders: palpitations.

Musculo-skeletal disorders: muscle cramps, hypotonia.

Other less frequently reported reactions include the following:

Cardiovascular disorders: angina pectoris, rhythm disturbances, orthostatic hypotension.

Gastrointestinal disorders: diarrhoea, sialorrhoea.

Musculo-skeletal disorders: leg pain, torsion dystonia.

Central and peripheral nervous system disorders: hallucinations, mania, agitation, confusion fainting.

Respiratory disorders: dyspnoea.

Reproductive disorders male and female: changes in libido.

Skin and appendages disorders: pruritus and rash may occasionally occur.

Disorders of the other special senses: isolated cases of loss or change of taste have been reported.

Blood disorders: haemolytic anaemia as well as mild, transient leukopenia and thrombocytopenia have been reported in a few rare cases (for monitoring see Special Precautions under *General).* Therefore, as in any long-term levodopa-containing treatment, blood count and liver and kidney function should be monitored periodically.

Urinary system disorders: urine may be altered in colour, usually red tinged and turns dark on standing.

Investigations:

Other body fluids or tissues may also be discoloured or stained including saliva, the tongue, teeth or oral mucosa.

Transient rises in AST, ALT and alkaline phosphatase are common. Increased gamma-glutamyltransferase has been reported. Serum urea and creatinine levels may fall early in treatment and then revert to normal after some months. PBI levels may rise. Transient rise in BSP retention. Prothrombin levels may rise. Transient fall in platelet and eosinophil count may occur.

Post-marketing: anxiety, delusions and temporal disorientation may occur particularly in elderly patients and in patients with a history of such disorders. Madopar is associated with somnolence and has been associated with excessive daytime somnolence and sudden sleep onset episodes.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms and signs

Symptoms and signs of overdose are qualitatively similar to the side effects of Madopar in therapeutic doses but may be of greater severity. Overdose may lead to: cardiovascular side effects (e.g. cardiac dysrhythmias), psychiatric disturbances (e.g. confusion and insomnia), gastro-intestinal effects (e.g. nausea and vomiting) and abnormal involuntary movements.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular patients may require symptomatic treatment for cardiovascular effects (e.g. anti-dysrhythmics) or central nervous system effects (e.g. respiratory stimulants, neuroleptics).

In addition, for the controlled release formulations further absorption should be prevented using an appropriate method.

Contact a poison centre for advice on management of overdosage.

IDENTIFICATION

Pale red, slightly speckled, cylindrical biconvex tablets.

Imprint: Upper face: ROCHE with hexagon, cross-break mark. Lower-face: cross-break mark.

PRESENTATION

Amber glass bottles containing 100 tablets.

STORAGE INSTRUCTIONS

Store below 25 °C and protect from light and moisture. Keep out of reach of children.

REGISTRATION NUMBER

P/5.4.1/150

NAME AND BUSINESS ADDRESS OF THE CERTIFICATE OF REGISTRATION HOLDER

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	Madopar 250mg tablets
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