SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Madopar® HBS Capsules

COMPOSITION

Madopar HBS (Hydrodynamically Balanced System – controlled release capsule) contains 100 mg levodopa and 25 mg benserazide (as hydrochloride).

Excipients: calcium hydrogen phosphate, gelatin, hydrogenated vegetable oil, indigo carmine, iron oxide yellow,magnesium stearate, mannitol, methyl hydroxypropylcellulose, povidone, talc, titanium dioxide, and TEKPRINT SW-1102 red ink used as a printing ink.

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.

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. Madopar HBS capsules are formulated to provide prolonged release of the active ingredients in the stomach, where the capsule remains for 3 - 6 hours. This provides therapeutic levodopa plasma levels for several hours and a reduction of the concentration peaks.

Pharmacokinetic properties

Absorption: The pharmacokinetic properties of Madopar HBS differ from those of the conventional tablets. The active ingredients are released slowly in the stomach. Maximum plasma concentrations of levodopa, which is 20 –30 % of that achieved with the standard dosage form, are reached approximately 3 hours after ingestion. The plasma concentration-time curve shows a longer “half-value duration” (time span during which plasma concentrations are equal to, or higher than, half the maximum concentration) than that of the conventional Madopar tablets, which indicates controlled release properties.

The bioavailability of Madopar HBS is 50 – 70 % of that of Madopar tablets, and is not affected by food. Maximum plasma concentrations of levodopa are not affected by food, but occur later (5 hours) and are lower, after postprandial administration of Madopar HBS, compared with Madopar tablets.

Co-administration of an antacid with Madopar HBS reduces the extent of levodopa absorption by 32 % (see INTERACTIONS).

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: Madopar HBS is indicated for patients presenting with all types of fluctuations (i.e. "peak dose dyskinesia" and "end of dose deterioration" such as nocturnal immobility).

CONTRAINDICATIONS

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

Madopar HBS must not be given in conjunction with monoamine oxidase (MAO) inhibitors. The same contra-indications apply as for sympathomimetic agents (such as epinephrine (adrenaline) and norepinephrine (noradrenaline) and their derivatives). Madopar HBS must not be given to patients with decompensated endocrine, renal or hepatic function, cardiac disorders, glaucoma, psychoses and highly pronounced psychoneuroses.

Madopar HBS must not be administered to patients under 25 years of age (skeletal development must be complete prior to Madopar HBS administration).

Pregnancy and Lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS

Neuroleptic malignant syndrome: Madopar HBS 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 HBS 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 antidiabetic 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 "CONTRA-INDICATIONS" 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 levodopa 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, anaesthesia with halothane, Madopar HBS should, be withdrawn 12-48 hours before surgical intervention, as fluctuations in blood pressure and/or dysrrhythmias may occur in patients on Madopar HBS 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 HBS 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 HBS. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore 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

Trihexyphenidyl given concomitantly with Madopar HBS does not affect the pharmacokinetics of levodopa.

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.

Combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO inhibition and hence they should not be given concomitantly with Madopar. (see also CONTRAINDICATIONS).

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 HBS 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 HBS 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 - Biochemical Abnormalities".

PREGNANCY AND LACTATION

Madopar HBS is absolutely contra-indicated 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 HBS treatment should not breastfeed their infants, since the occurrence of skeletal malformations in the infants cannot be excluded.

DOSAGE AND DIRECTIONS FOR USE

Madopar HBS capsules must not be opened before ingestion because the controlled release characteristics will be lost!

Method of administration: When taking Madopar HBS, patients must always ensure that they swallow the capsule whole, without chewing it. Since absorption may be impaired by food intake (see PHARMACOLOGICAL ACTION - Pharmacokinetics), Madopar HBS 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 HBS with some food or liquid.

Patients who experience large fluctuations in the effect of Madopar 250 mg tablets during the course of the day (on-off phenomena), should receive smaller, more frequent single doses, be switched to Madopar HBS, or use alternative medication (see below Special dosage instructions).

The switch from Madopar tablets to Madopar HBS is preferably made from one day to the next, beginning with the morning dose. The daily dose and dosing interval should initially be the same as with Madopar tablets. After 2 to 3 days, the dosage should be gradually increased by about 50 %, because of the lower bioavailability of Madopar HBS. Patients should be informed that their condition may temporarily deteriorate.

Due to the pharmacokinetic properties of Madopar HBS, the onset of action is approximately 3 hours compared to Madopar tablets. If desired, effective plasma levels may be achieved more rapidly by administering Madopar HBS together with Madopar tablets. This may prove especially useful for the first morning dose, which should preferably be somewhat higher than the subsequent daily doses. The individual titration for Madopar HBS must be carried out slowly and carefully, in intervals of at least 2 to 3 days between each change of dosage.

In patients with nocturnal immobility, positive effects have been reported after gradually increasing the last evening dose to up to 3 capsules of Madopar HBS at bedtime. Patients should be carefully observed for possible psychiatric side-effects. Over-responsiveness to Madopar HBS (dyskinesia) may be controlled by increasing the length of the intervals between administrations rather than by

reducing the single doses. In case of poor response to Madopar HBS, it is preferable to resume the previous treatment with Madopar tablets.

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

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: pruritius 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 (see Side Effects).

If a patient has taken an overdose of the controlled release form, Madopar HBS capsules, occurrence of symptoms and signs may be delayed due to delayed absorption of the active substances from the stomach.

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. antidysrhythmics) 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

Opaque dark green (cap) and light blue (body) capsules with an imprint Roche, containing white to trace-yellowish, fine granular powder.

PRESENTATION

Amber glass bottles containing 30 or 100 tablets.

STORAGE INSTRUCTIONS

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

REGISTRATION NUMBER

31/5.4.1/0194

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