PACK INSERT FOR MALAYSIA

Madopar®

Levodopa + Benserazide

For the treatment of parkinsonian patients

Composition

Active ingredient: Madopar is a combination of levodopa and the decarboxylase inhibitor benserazide (as hydrochloride) in the ratio of 4:1.

Excipients: Madopar contains the colorants indigotine (E 132), titanium dioxide (E 171) or iron oxide (E 172) depending on the formulation.

The preparation is available as capsules of three different strengths, as cross-scored tablets of two different strengths, as dispersible tablets of two different strengths and as capsules with a controlled-release action:

Madopar '62.5'(blue and light grey capsules) with 50 mg levodopa + 12.5 mg benserazide (as hydrochloride);

Madopar '125' (blue and pink capsules) with 100 mg levodopa + 25 mg benserazide (as hydrochloride);

Madopar '250' (blue and brown capsules) with 200 mg levodopa + 50 mg benserazide (as hydrochloride);

Madopar '125' cross scored (pink tablets) with 100 mg levodopa + 25 mg benserazide (as hydrochloride);

Madopar '250' cross scored (pink tablets) with 200 mg levodopa + 50 mg benserazide (as hydrochloride);

Madopar 'dispersible 62.5' scored (off-white tablets) with 50 mg levodopa + 12.5 mg benserazide (as hydrochloride);

Madopar 'dispersible 125' scored (off-white tablets) with 100 mg levodopa + 25 mg benserazide (as hydrochloride);

Madopar HBS (Hydrodynamically Balanced System) (controlled-release green and light blue capsules) with 100 mg levodopa + 25 mg benserazide (as hydrochloride).

Madopar HBS capsules must not be opened or chewed before swallowing because the controlled-release characteristics will be lost!

Pharmacological Properties and Effects

Pharmacotherapeutic group: Anti-parkinson drugs, ATC code: N04BA02

Pharmacodynamics Properties

Mechanism of Action

Dopamine, which acts as a neurotransmitter in the brain, is not present in sufficient quantities in the basal ganglia of parkinsonian patients. 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 extracerebral as well as cerebral tissues. As a result, most of the levodopa administered is not available to the basal ganglia, and the dopamine produced peripherally frequently causes unwanted effects. It is therefore particularly desirable to inhibit extracerebral decarboxylation of levodopa. This can be achieved by simultaneous administration of levodopa and benserazide, a peripheral decarboxylase inhibitor.

Madopar is a combination of these two substances in a ratio of 4:1 - this ratio having proved optimal in clinical trials and therapeutic use - and is just as effective as large doses of levodopa given alone.

Madopar dispersible tablets are especially suitable for patients with dysphagia (difficulties in swallowing) or who require a formulation with a more rapid onset of action, e.g. patients suffering from early morning and afternoon akinesia or who exhibit "delayed on" or "wearing off" phenomena.

Madopar HBS is a special formulation providing prolonged release of the active ingredients in the stomach where the capsule remains for 3-6 hours. The stomach thus serves as a reservoir for the drugs.

Pharmacokinetics Properties

Absorption

Standard forms

Levodopa is mainly absorbed from the upper regions of the small intestine, and absorption there is independent of the site. Maximum plasma concentrations of levodopa are reached approximately one hour after ingestion of standard Madopar. The absolute bioavailability of levodopa from standard Madopar is 98% (range 74-112%). Capsules and tablets of standard Madopar are bioequivalent.

The maximum plasma concentration of levodopa and the extent of levodopa absorption (AUC) increase proportionally with dose (50-200 mg levodopa).

Food intake reduces the rate and extent of levodopa absorption. The peak levodopa plasma concentration is 30% lower and occurs later when standard Madopar is administered after a standard meal. The extent of levodopa absorption is reduced by 15%.

Dispersible form

The pharmacokinetic profiles of levodopa following administration of Madopar dispersible in healthy volunteers and parkinsonian patients are very similar to those following administration of standard Madopar, but time to peak concentrations tends to be shorter after Madopar dispersible. There is less interindividual variability in absorption parameters for Madopar dispersible taken as a suspension.

Controlled release form

The pharmacokinetic properties of Madopar HBS differ from those of standard Madopar (capsules, tablets) and dispersible form. The active ingredients are released slowly in the stomach. Maximum plasma concentrations of levodopa, which are 20-30% of those achieved with the standard dosage forms, are reached about 3 hours after administration. The plasma concentration-time curve shows a longer 'half-value duration' (time span during which plasma concentrations are equal to or exceed half the maximum concentration) than with standard Madopar, which indicates pronounced controlled-release properties. The bioavailability of Madopar HBS is 50-70% of that of standard Madopar and is not affected by food. Maximum plasma concentrations of levodopa are not affected by food, but occur later (5 hours) after postprandial administration of Madopar HBS.

Distribution

Levodopa crosses the gastric mucosa and the blood-brain barrier by a saturable transport system. It is not bound to plasma proteins and its volume of distribution is 57 liters. 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 intestine and liver.

Metabolism

Levodopa is metabolized 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 hours and it accumulates in patients who receive therapeutic doses of Madopar.

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 acid, dihydroxyphenylacetic 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 (approximately 25%) in elderly patients (65 –78 years of age) with Parkinson's disease. The clearance of levodopa from plasma is about 430 ml/min.

Benserazide is almost entirely eliminated by metabolism. The metabolites are mainly excreted in the urine (64%) and to a smaller extent in feces (24%).

Pharmacokinetic in Special Populations

No pharmacokinetic data are available in uremic and hepatic patients.

Effect of age on the pharmacokinetics of levodopa

In older Parkinsonian patients (65-78 years of age) both the elimination half-life and the AUC of levodopa is about 25% higher than in younger patients (34-64 years of age). The statistically significant age effect is clinically negligible and is of minor importance for the dosing schedule of any indication.

Indications

Madopar is indicated for the treatment of all forms of Parkinson's syndrome with the exception of drug-induced parkinsonism.

Madopar dispersible is a special formulation for patients with dysphagia (difficulties in swallowing) or who require a formulation with a more rapid onset of action, e.g. patients suffering from early morning and afternoon akinesia, or who exhibit "delayed on" or "wearing off" phenomenon.

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

Dosage and administration

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

In the early stages of parkinsonism it is advisable to start treatment with 1 capsule of Madopar '62.5' or ½ tablet of Madopar '125' three to four times daily. As soon as tolerability of the initial dosing schedule is confirmed, the dosage should be increased slowly in accordance with the patient's response.

An optimal effect is generally achieved with a daily dosage of Madopar corresponding to 300-800 mg levodopa + 75-200 mg benserazide, to be divided into 3 or more doses. Between 4 and 6 weeks may be needed to achieve the optimal effect. If it proves necessary to further increase the daily dosage, this should be done on a monthly basis.

Maintenance therapy

The average maintenance dosage is 1 capsule or tablet of Madopar '125' 3-6 times daily. The number of individual doses (not less than 3) and their distribution throughout the day must be titrated for optimal effect. Madopar HBS and Madopar dispersible may substitute standard Madopar to achieve an optimal effect.

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 drugs may need to be reduced or these drugs gradually withdrawn.

Madopar dispersible tablets are particularly suitable for patients with dysphagia (difficulties in swallowing) or in situations where a more rapid onset of action is required e.g. patients suffering from early morning and afternoon akinesia, or who exhibit "delayed on" or "wearing off" phenomenon.

Patients who experience large fluctuations in the drug's effect in the course of the day (on-off phenomena) should receive smaller, more frequent single doses, or be switched to Madopar HBS.

The switch from standard Madopar 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 standard Madopar.

After 2-3 days, the dosage should be gradually increased by about 50%. Patients should be informed that their condition may temporarily deteriorate.

Due to the pharmacokinetic properties of Madopar HBS, the onset of action is delayed. The clinical effect may be achieved more rapidly by administering Madopar HBS together with standard Madopar or Madopar dispersible. This may prove especially useful for the first morning dose, which should preferably be higher than the subsequent daily doses. The individual titration for Madopar HBS must be carried out slowly and carefully, allowing intervals of at least 2-3 days between dose changes.

In patients with nocturnal immobility, positive effects have been reported after gradually increasing the last evening dose up to 250 mg of Madopar HBS on retiring.

Excessive responses to Madopar HBS (dyskinesia) can be controlled by increasing the interval between doses rather than reducing the single doses.

Treatment with standard Madopar or Madopar dispersible should be resumed if the response to Madopar HBS is inadequate.

Patients should be carefully observed for possible undesirable psychiatric symptoms.

Renal Impairment

Levodopa and benserazide are both extensively metabolized and less than 10% of levodopa is excreted unchanged through the kidneys. No dose reduction is therefore necessary in case of mild or moderate renal insufficiency.

Pharmacokinetic (PK) data with levodopa in renal impaired patients are not available.

Madopar is well tolerated by uremic patients undergoing hemodialysis.

Hepatic Impairment

Levodopa is mainly metabolized by the aromatic amino acid decarboxylase that is abundantly present in the intestinal tract, in kidney and heart in addition to the liver.

PK data with levodopa in hepatic impaired patients are not available.

Method of administration

When taking standard Madopar capsules or Madopar HBS, patients must always ensure that they swallow the whole capsule without chewing it.

Standard Madopar tablets may be broken into small pieces to facilitate swallowing.

Madopar dispersible tablets are to be dispersed in a quarter of a glass of water (approx. 25-50 ml). The tablets dissolve completely, producing a milky-white dispersion within a few minutes. Because of rapid sedimentation, it is advisable to stir the dispersion before drinking. Madopar dispersible tablets should be taken within half an hour of dissolving the tablet.

Where possible, Madopar should be taken at least 30 minutes before or 1 hour after meals, so that the competitive effect of dietary protein on levodopa uptake can be avoided. . Undesirable gastrointestinal effects, which may occur mainly in the early stages of the treatment, can largely be controlled by taking Madopar with some food or liquid or by increasing the dose slowly.

Contraindications

Madopar is contraindicated in:

- patients with known hypersensitivity to levodopa or benserazide or any of the excipients.
- patients receiving non-selective monoamine oxidase (MAO) inhibitors due to the risk of hypertensive crisis. However, selective MAO-B inhibitors, such as selegiline and rasagiline, or selective MAO-A inhibitors, such as moclobemide, are not contraindicated. Combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO inhibition, and hence this combination should not be given concomitantly with Madopar (see Interactions).
- patients with decompensated endocrine, renal (except Restless Legs Syndrome (RLS) patients on dialysis) or hepatic function, cardiac disorders, psychiatric diseases with a psychotic component or closed angle glaucoma.
- patients less than 25 years old (skeletal development must be complete).
- pregnant women or to women of childbearing potential in the absence of adequate contraception (see Pregnancy, nursing mothers). If pregnancy occurs in a woman taking Madopar, the drug must be discontinued. (as advised by the prescribing physician).

Warnings and Precautions

General

Warnings related to immunological reactions

Hypersensitivity reactions may occur in susceptible individuals.

Warnings related to neurological and psychiatric effects

Madopar must not be withdrawn abruptly. Abrupt withdrawal of the preparation may result in a neuroleptic malignant-like syndrome (hyperpyrexia and muscular rigidity, possibly 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, hospitalized and rapid and appropriate symptomatic treatment given. This may include resumption of Madopar therapy after an appropriate evaluation.

Patients should be carefully observed for possible undesirable psychiatric.

Depression may occur in patients treated with Madopar, but may also be an effect of the underlying disease

Levodopa 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 levodopa. 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 *(Ability to drive and use machines)*.

Dopaminergic drugs

Impulse control disorders such as pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's Disease. There is no established causal relationship between Madopar, which is not a dopamine agonist, and these events. However, caution is advised as Madopar is a dopaminergic drug.

Warnings related to ocular effects

Regular measurement of intraocular pressure is advisable in patients with open-angle glaucoma, as levodopa theoretically has the potential to raise intraocular pressure.

Warnings related to Interactions

If a patient on levodopa requires a general anaesthesia, 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 should be discontinued 12-48 hours before surgical intervention as fluctuations in blood pressure and/or arrhythmias may occur in patients on Madopar therapy. Madopar therapy may be resumed following surgery; the dosage should be increased gradually to the preoperative level.

Laboratory Tests

Checks of liver function and blood cell count should be performed during treatment.

Patients with diabetes should undergo frequent blood sugar tests, and the dosage of antidiabetic agents should be adjusted to blood sugar levels.

Potential for Drug Dependence or Abuse

Dopamine dysregulation syndrome (DDS): A small number of patients suffer from cognitive and behavioural disturbance 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

Ability to drive and use machines

Madopar may have a major influence on the ability to drive and use machines.

Patients being treated with levodopa 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.

Interactions with other Medicinal Products and other Forms of Interaction

Pharmacokinetic interactions

Coadministration of the anticholinergic drug trihexyphenidyl with standard Madopar reduces the rate, but not the extent, of levodopa absorption. Trihexyphenidyl given concomitantly with Madopar HBS does not affect the pharmacokinetics of levodopa.

Coadministration of antacids with Madopar HBS reduces the extent of levodopa absorption by 32%.

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 as a result of increased absorption of levodopa in the intestine.

Pharmacodynamic interactions

Neuroleptics, opioids and antihypertensive medications containing reserpine inhibit the action of Madopar.

If Madopar is to be administered to patients receiving irreversible non-selective MAO inhibitors, an interval of at least 2 weeks should be allowed between cessation of the MAO inhibitor and the start of Madopar therapy. Otherwise unwanted effects such as hypertensive crises are likely to occur (see Contraindications).

Selective MAO-B inhibitors, such as selegiline, and rasagiline and selective MAO-A inhibitors, such as moclobemide, can be prescribed to patients on Madopar therapy; it is recommended to readjust the levodopa dose to the individual patient's needs, in terms of both efficacy and tolerability. Combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO inhibition and hence this combination should not be given concomitantly with Madopar (see Contraindications).

Madopar should not be administered concomitantly with sympathomimetics (agents such as epinephrine, norepinephrine, isoproterenol or amphetamine which stimulate the sympathetic nervous system) as levodopa may potentiate their effects. Should concomitant administration prove necessary, close surveillance of the cardiovascular system is essential, and the dose of the sympathomimetic agents may need to be reduced.

Combination with other agents such as anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists is permissible, though both the desired and the undesired effects of treatment may be intensified. It may be necessary to reduce the dosage of Madopar or the other substance.

When initiating an adjuvant treatment with a COMT inhibitor, a reduction of the dosage of Madopar may be necessary.

Anticholinergics should not be withdrawn abruptly when Madopar therapy is instituted, as levodopa does not begin to take effect for some time.

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

General anaesthesia with halothane: Madopar should be discontinued 12-48 hours before surgical intervention requiring general anaesthesia with halothane as fluctuations in blood pressure and/or arrhythmias may occur.

For general anaesthesia with other anesthetics see section *Warning and Precautions*.

Laboratory test interactions

Levodopa may affect the results of laboratory tests for catecholamines, creatinine, uric acid and glucose. The urine test results can be false positive for ketone bodies.

Coombs' tests may give a false-positive result in patients taking Madopar.

Food interactions

A diminution of effect is observed when the drug is taken with a protein-rich meal.

Levodopa is a large neutral amino acid (LNAA) and it competes with LNAAs from dietary protein for transport across the gastric mucosa and blood-brain barrier.

Pregnancy, nursing mothers

Madopar is contraindicated during pregnancy and in women of childbearing potential in the absence of adequate contraception (see Contraindications).

Since it is not known whether benserazide passes into breast milk, mothers requiring Madopar treatment should not nurse their infants, since the occurrence of skeletal malformations in the infants can not be excluded.

Undesirable effects

Post Marketing Experience

The following adverse reactions have been identified from post marketing experience with Madopar (Table 2) based on spontaneous case reports and literature cases.

The corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (these reactions are reported voluntarily from a population of uncertain size, therefore it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure).

Table 1 Adverse Drug Reactions from post marketing experience

Adverse Drug Reactions	Frequency category
Blood and Lymphatic System Disorders[1]:	
Haemolytic anaemia	not known
Transient leukopenia	not known
Thrombocytopenia	not known
Metabolic and nutritional disorders:	
Anorexia	not known
Psychiatric Disorders:	
Depression	not known
Agitation	not known
Anxiety	not known
Insomnia	not known
Hallucinations	not known
Delusions	not known
Temporal disorientation	not known
Dopamine dysregulation syndrome (DDS)	not known
Nervous System Disorder:	
Ageusia	not known
Dysgueusia	not known
Dyskinesia (choreiform and athetotic)	not known
Fluctuations in therapeutic response -Freezing episodes - end-of-dose deterioration - "on-off" effect	not known
Augmentation of RLS	not known
Somnolence	not known
Excessive daytime sleepiness	not known
Sudden sleep onset episodes	not known
Cardiac disorders:	
Cardiac arrhythmias	not known
Vascular Disorders:	
Orthostatic hypotension	not known
Gastrointestinal disorders:	

Nausea	not known
Vomiting	not known
Diarrhoea	not known
Saliva discolouration	not known
Tongue discolouration	not known
Tooth discolouration	not known
Oral mucosa discolouration	not known
Skin and subcutaneous tissue disorders:	
Pruritus	not known
Rash	not known
Liver and Biliary disorders:	
Transaminases increased	not known
Alkaline phosphatase increase	not known
Gamma-glutamyltransferase increased	not known
Renal and urinary disorders:	
Chromaturia	not known
Blood urea nitrogen increased	not known

[1]*See section Warnings and Precautions, Laboratory Tests*

Blood and Lymphatic System Disorders*:* Haemolytic anemia, transient leukopenia and thrombocytopenia have been reported. In any long-term levodopa-containing treatment, blood cell count and liver and kidney function should be monitored periodically.

Psychiatric Disorders: Depression can be part of the clinical picture in patients with Parkinson's disease and may also occur in patients treated with Madopar. Agitation, anxiety, insomnia, hallucinations, delusions and temporal disorientation may occur particularly in elderly patients and in patients with a history of such disorders.

Nervous System Disorder: At later stages of the treatment, dyskinesia (e.g. choreiform or athetotic) may occur. These can usually be eliminated or be made tolerable by a reduction of dosage. With prolonged treatment, fluctuations in therapeutic response may also be encountered. They include freezing episodes, end-of-dose deterioration and the "on-off" effect. These can usually be eliminated or made tolerable by adjusting the dosage and by giving smaller single doses more frequently. An attempt at increasing the dosage again can subsequently be made in order to intensify the therapeutic effect. Madopar is associated with somnolence and has been associated very rarely with excessive daytime sleepiness and sudden sleep onset episodes.

Vascular Disorders: Orthostatic disorders commonly improve following reduction of the Madopar dosage.

Gastrointestinal disorders: Undesirable gastrointestinal effects, which may occur mainly in the early stages of the treatment, can largely be controlled by taking Madopar with protein snack or liquid or by increasing the dose slowly.

Investigations: Urine may be altered in colour, usually acquiring a red tinge which turns dark on standing. Other body fluids or tissues may also be discoloured or stained including saliva, the tongue, teeth or oral mucosa.

Overdosage

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 arrhythmias), psychiatric disturbances (e.g. confusion and insomnia), gastro-intestinal effects (e.g. nausea and vomiting) and abnormal involuntary movements (see 2.6.1 Post Marketing [Undesirable Effects]).

If a patient has taken an overdose of a controlled release form of Madopar (i.e. 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. antiarrhythmics) 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.

Stability

This medicine should not be used after the expiry date (EXP) shown on the pack. See also outer pack for storage remark.

Madopar dispersible should be taken within half an hour of dissolving the tablet.

Packs

Madopar '125'	Capsules with 100 mg levodopa + 25 mg benserazide	100
Madopar '250'	Tablets (cross-scored) with 200 mg levodopa + 50 mg benserazide	100
Madopar HBS	Capsules with 100 mg levodopa + 25 mg benserazide	30, 100

Medicine: keep out of reach of children

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