Madopar®

Levodopa + Bensirazide

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1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug
ATC code: N04BA02
Madopar is a combination of levodopa and the decarboxylase inhibitor benserazide.

1.2 Type of Dosage Form
Dispersible form:
Single-scored dispersible tablets as Madopar '125'.

1.3 Route of Administration
Oral.

1.4 Sterile/Radioactive Composition
Not applicable.

1.5 Qualitative and Quantitative Composition
Active ingredients:
Madopar is a combination of levodopa and the decarboxylase inhibitor benserazide (as hydrochloride) in a ratio of 4:1. The following strength is available: Madopar '125'=levodopa 100 mg + benserazide 25 mg.

Excipients: citric acid (anhydrous), pregelatinised starch (maize), microcrystalline cellulose, magnesium stearate.

2. CLINICAL PARTICULARS
2.1 Therapeutic Indications
Madopar is indicated in the treatment of Parkinson's disease, symptomatic parkinsonism postencephalitic, except drug-induced parkinsonism syndromes.

Madopar dispersible is a formulation which is 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.

2.2 Dosage and Administration
Where possible, Madopar should be taken 30 min before or one hour after meals where possible so that the competitive effect of dietary protein on levodopa uptake can be avoided (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*) and to facilitate a more rapid onset of action. Undesirable gastrointestinal effects, which may occur mainly in the early stages of the treatment, can largely be controlled by taking Madopar with a low protein snack (e.g. biscuits) or liquid or by increasing the dose slowly.

Method of Administration
Madopar dispersible tablets are to be dispersed in a quarter of a glass of water (approx. 25-50 mL). The tablets disintegrate 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 preparing the dispersion.

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 half a tablet of Madopar 125 mg three to four times daily. The daily dosage is then increased by 1 tablet of Madopar 125 mg 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 1 tablet Madopar 125 mg twice a week. Thus, the effective dosage may be reached in 4 days. The effective dosage is generally between 4 and 8 tablets of Madopar 125 mg daily, divided into three or four doses; it is rarely necessary to administer more than 10 tablets of Madopar 125 mg daily.

Example: Madopar 125 mg tablet intake

	Morning	**Noon**	**at 4 pm**	**Night**	**Total per Day**
1st Week	1	1	-	1	3
2nd Week	1	1	1	1	4
3rd Week	2	1	1	1	5
4th and 5th Week	2	2	1	1	6

If there is no satisfactory improvements, increase the dosage but with slower (administration).

	Morning	**Noon**	**at 4 pm**	**Night**	**Total per Day**
6th and 7th Week	2	2	2	1	7
8th and 9th Week	2	2	2	2	8

If a dose of greater than 8 tablets Madopar 125 mg is necessary, any such increment may be conducted only with one month interval.

In rare cases where the recommended single dose under the above plan is too high, it is recommended to change from 1 to just ½ tablet, whilst the administration shall continue according to the total daily dose.

Maintenance Therapy
In all cases it is essential to divide the daily dosage into at least three doses. The average maintenance dosage is 2 tablets Madopar 125 mg three times a day. 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. If a patient begins to experience marked fluctuation in response during the day (e.g. 'on-off' phenomena), sometimes the situation can be noticeably improved by administering ½ tablet Madopar 125 mg. The daily dosage is not changed, although some (or, if necessary, all), of the tablets Madopar 125 mg are replaced by ½ tablet of Madopar 125 mg, which should be taken at shorter intervals.

2 x ½ tablets of Madopar 125 mg taken in two divided doses instead of 1 tablet of Madopar 125 mg. 4 x ½ tablets of Madopar 125 mg taken in four divided doses instead of 2 tablets of Madopar 125 mg.

Changing from Levodopa to Madopar
Where it proves judicious to give Madopar to patients who have up until then been treated with levodopa, the changeover can be effected from day-1 to the next as follows:

- The patient should be initiated on a total of one less Madopar 125 mg dispersible tablet daily than the total number of 500 mg levodopa tablets or capsules previously taken.

For example, if the patient had previously taken 2 g levodopa daily, then he should start on three dispersible tablets Madopar 125 mg daily on the following day. A minimum initial dosage of 1 tablet of Madopar 125 mg 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 schedule is identical with that for patients not previously treated with levodopa). If a deterioration in the patient's clinical condition is observed, the dosage may be increased earlier.

2.2.1 Special Dosage Instructions

Renal Impairment
See sections *2.3 Contraindications, 2.5.6 Renal Impairment*.

Hepatic Impairment
The safety and efficacy of Madopar have not been established in patients with hepatic impairment (see sections *2.3 Contraindications, 2.5.6 Hepatic Impairment*).

General Remarks
In the rare cases in which 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: Such as by 1 tablet of Madopar 125 mg every 2 or 3 weeks only. The recommended interval between dosage increases is longer when the average effective dosage of 6 tablets of Madopar 125 mg daily is exceeded, since it may take some time for the full therapeutic effect of the drug to develop. Like all replacement therapy, treatment with Madopar is long-term. If, after about 4 weeks, signs of (even slight) improvement in the symptoms are detectable, treatment with Madopar should be continued in order to ensure further uninterrupted improvement. Sometimes, up to 6 months is required for Madopar to achieve maximum efficacy.

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

2.3 Contraindications
The same contraindications as for sympathomimetic drugs such as epinephrine, norepinephrine and their derivatives.

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 (see section *2.4.1 Warnings and Precautions, General*). 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 section *2.4.5 Interactions with Other Medicinal Products and Other Forms of Interaction*).
- patients with decompensated endocrine, renal 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 women of childbearing potential in the absence of adequate contraception (see sections *2.5.2 Pregnancy* and *2.5.3 Lactation*). If pregnancy occurs in a woman taking Madopar, the drug must be discontinued (as advised by the prescribing physician).

2.4 Warnings and Precautions

2.4.1 General

Periodic cardiovascular checks (including ECG) should be performed in all patients with a history of myocardial infarction, coronary insufficiency or cardiac arrhythmia.

Patients with history of gastric ulcer or osteomalacia should be kept under close observation. However, concomitant therapy with antihypertensive agents is quite permissible, provided the blood pressure is monitored regularly (possibility of an additive effect).

Warning 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 symptoms.

Depression can be part of the clinical picture in patients with Parkinson's disease and may also occur in patients treated with Madopar.

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 (see section *2.4.3 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.

It is better not to give monoamine oxidase inhibitors for patients while under treatment with Madopar. Madopar may strengthen the effect of sympathomimetic drugs concurrently administered. It is necessary therefore to conduct close surveillance of the cardiovascular system, and the dose of the sympathomimetic agents may need to be reduced. Other antiparkinsonian medication should not be abruptly discontinued as soon as Madopar therapy begins, since the effect of Madopar often becomes evident only after a latent period. In certain cases, the dosage of the other antiparkinsonian drugs may be progressively reduced later on.

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. Anesthesia with cyclopropane or halothane should be avoided in emergency surgery. Patients who are to undergo surgery should be very closely monitored.

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 crisis are likely to occur (see sections *2.3 Contraindications* and *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

Concomitant administration of antipsychotics with dopamine-receptor blocking properties, particularly D2-receptor antagonists might antagonize the antiparkinsonian effects of levodopa-benserazide. Levodopa may reduce antipsychotic effects of these drugs. These drugs should be co-administered with caution (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

Madopar should not be administered concomitantly with sympathomimetics (such as epinephrine, norepinephrine, isoproterenol or amphetamine) 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 (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

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.

Combination with 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 (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

Laboratory tests
Checks of liver function and blood cell count should be performed during treatment (see section *2.6.2 Postmarketing Experience*). Patients with diabetes should undergo frequent blood sugar tests, and the dosage of antidiabetic agents should be adjusted to blood sugar levels.

2.4.2 Drug Dependence and 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.

2.4.3 Ability to Drive and Use Machines
Madopar may have a major influence on 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 (see section *2.4.1 General*).

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential
Fertility
No fertility studies have been performed (see section *3.3 Nonclinical Safety*).

Pregnancy testing
A pregnancy test prior treatment is recommended to exclude pregnancy.

Contraception
Adequate contraception should be used in women of childbearing potential during treatment with Madopar.

2.5.2 Pregnancy
Madopar is contraindicated during pregnancy and in women of childbearing potential in the absence of adequate contraception (see sections *2.3 Contraindications*, *3.3.4 Reproductive Toxicity* and *3.3.5 Other*).

If pregnancy occurs in a woman taking Madopar, the drug must be discontinued (as advised by the prescribing physician).

Labor and Delivery
The safe use of Madopar during labor and delivery has not been established.

2.5.3 Lactation
The safe use of Madopar during lactation has not been established.

It is not known whether benserazide is excreted in human breast milk. Mothers requiring Madopar treatment should not nurse their infants, as the occurrence of skeletal malformations in the infants can not be excluded.

2.5.4 Pediatric Use
Madopar is contraindicated in patients less than 25 years old (see section *2.3 Contraindications*).

2.5.5 Geriatric Use
See section *3.2.5 Pharmacokinetics in Special Populations*.

2.5.6 Renal Impairment
Levodopa and benserazide are both extensively metabolised and less than 10% of levodopa is excreted unchanged through the kidneys (see section 2.*2.1 Special Dosage Instructions*).

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

2.5.7 Hepatic Impairment
Levodopa is mainly metabolised by the aromatic amino acid decarboxylase that is abundantly present in the intestinal tract, in kidney and heart in addition to the liver (see section *2.2.1 Special Dosage Instructions*).

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

2.6 Undesirable Effects

2.6.1 Clinical Trials
Parkinson's disease:
No text.

2.6.2 Postmarketing Experience
The following adverse reactions have been identified from postmarketing experience with Madopar (Table 1) 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), 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 postmarketing 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:	

Adverse Drug Reactions	Frequency Category
Ageusia	not known
Dysgeusia	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 *2.4.1 Warnings and Precautions, Laboratory Tests*

Blood and Lymphatic System Disorders: Haemolytic anaemia, 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 a low 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.

2.7 Overdose

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 section *2.6.2 Postmarketing Experience, (Undesirable Effects)*).

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.

2.8 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.

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 crisis are likely to occur (see section *2.3 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 section *2.3 Contraindication*s).

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.

Since additive effect may occur in concomitant administration of Madopar with antihypertensives, therefore a regular monitoring of blood pressure should be conducted.

Combination with 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 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 anesthesia with other anaesthetics see section *2.4.1 General (Warnings and Precautions).*

Laboratory test interactions

Levodopa may affect the results of laboratory tests for catecholamines, creatinine, uric acid and glycosuria. 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Dopamine, which acts as a neurotransmitter in the 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 metabolized to dopamine by aromatic L-amino acid decarboxylase.

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.

3.1.2 Clinical/Efficacy Studies

No text.

3.1.3 Immunogenicity

Not applicable.

3.2 Pharmacokinetics Properties

3.2.1 Absorption

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.

3.2.2 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.

3.2.3 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.

3.2.4 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 geriatric patients (65–78 years of age) with Parkinson's disease (see section *3.2.5 Pharmacokinetic in Special Population*). 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%).

3.2.5 Pharmacokinetics 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.

3.3 Nonclinical Safety
3.3.1 Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of Madopar.

3.3.2 Mutagenicity
Madopar and its constituents (levodopa and benserazide) were not observed to be mutagenic in the Ames test. No further data are available.

3.3.3 Impairment of Fertility
No fertility studies on animals have been performed to evaluate the effect of Madopar.

3.3.4 Reproductive Toxicity
Teratogenicity studies showed no teratogenic effects or effects on skeletal development in mice (400 mg/kg), rats (600 mg/kg; 250 mg/kg) and rabbits (120 mg/kg, 150 mg/kg).

At maternally toxic dose levels, intrauterine deaths increased (rabbits) and/or fetal weight decreased (rats).

3.3.5 Other
General toxicological studies in rats have shown the possibility of disturbed skeletal development.

No further animal data of relevance are available.

4. PHARMACEUTICAL PARTICULARS
4.1 Storage
This medicine should not be used after the expiry date (EXP) shown on the pack.

Madopar should be stored in its original package.
The bottle should be kept tightly closed, to protect from moisture.
Keep at temperature not exceeding 30°C, avoid humid place, recap the bottle properly with its drying agent.

4.2 Special Instruction for Use, Handling and Disposal
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Packaging
Madopar 125 mg dispersible tablets
No. Reg.: DKI1857507581A1
Box, bottle @ 30 dispersible tablets

Medicine: keep out of reach of children
Obat: Jauhkan dari jangkauan anak-anak
On medical prescription only
Harus dengan resep dokter

Manufactured by:
Delpharm Milano S.r.l, Segrate, Italy
for F. Hoffmann – La Roche Ltd., Basel, Switzerland

Imported by:
PT Boehringer Ingelheim Indonesia, Bogor, Indonesia

Distributed by:
PT Roche Indonesia, Jakarta, Indonesia

(This PI draft has been reviewed and approved for submission by Fairuz on 02-Jun-2021)