Combined administration of levodopa and bensera-
zyme thus makes it possible to compensate for dopa-
mine deficiency in the brain.

Pharmacokinetics

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.

Distribution
The combined use of levodopa and benserazide compensates the dopamine deficiency in the brain. At therapeutic doses, benserazide does not pene-
trate the blood-brain barrier.

Metabolism
Cerebral decarboxylase converts levodopa to dopamine, which in turn is converted-to a minor degree-to norepinephrine and-to a greater part-to inactive metabolites.

Benserazide is hydroxylated into trihydrobenzylhy-
drazine in the intestinal mucosa and the liver.

Elimination
The elimination half-life of levodopa is approximately 45 minutes.

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

Contraindications
Madopar must not be used in patients with known hypersensitivity to any of its ingredients. Patients should not be given monoamine oxidase inhibi-
tors except selegiline while under treatment with Madopar. Madopar must not be given to patients with severely decompensated endocrine, renal,
hepatic or cardiac disorders, psychoses or severe psychoneurses. Madopar must not be given to patients less than 25 years old (skeletal development must be complete) or to pregnant women. Madopar is contraindicated in patients with narrow-angle glaucoma.

**Side Effects**

Anorexia, nausea and vomiting are rare when Madopar is used. Such side effects, which may occur in the early stages of treatment, can be largely brought under control by taking Madopar during meals or together with sufficient food or liquid, and by increasing the dosage slowly. Cardiovascular disorders (e.g. cardiac arrhythmias or orthostatic hypotension) may infrequently occur. At later stages of treatment, involuntary (e.g. choreiform or athetotic) movements may occur. These can usually be eliminated or be made tolerable by a reduction of dosage. A subsequent further stepping-up of dosage in order to intensify the therapeutic effect may be attempted, since the side effects will not necessarily recur. Elevation of transaminase and alkaline phosphatase levels—though generally slight and not exceeding the upper limit of normal—has occasionally been observed. Hemolytic anemia, as well as mild, transient leukopenia and thrombocytopenia have also been reported in a few rare cases. Therefore, as in any long-term treatment, periodic blood counts should be made and liver and kidney function be tested. Mental disturbances (insomnia, agitation or, more rarely, depressive and—particularly in older patients—psychotic reactions) may be observed.

**Precautions**

Intraocular pressure should be measured regularly during Madopar treatment in patients with wide-angle glaucoma. Periodic cardiovascular checks (including ECG) should be performed in all patients with a history of myocardial infarction, coronary insufficiency or cardiac arrhythmia. Care should also be taken in patients with a history of gastric ulcer or osteomalacia. Other than in emergencies, Madopar therapy should be discontinued 1248 hours before surgical interventions requiring general anesthesia (see Drug Interactions). After surgery, medication with Madopar may be resumed, gradually increasing the dosage to the pre-operative level. If a patient must undergo surgery without Madopar having been withdrawn (e.g. in an emergency), anesthesia with cyclopropane or halothane should be avoided. Madopar should not be administered to patients with malignant melanoma (suspicious, undiagnosed lesions or evidence of melanoma in the history).

**Pregnancy and Lactation**

Animal studies have revealed fetotoxic effects, and no controlled trials have been conducted in man. The product must not be administered to pregnant women or nursing mothers. Women who become pregnant while being treated with Madopar must discontinue treatment immediately.

**Overdosage**

The most common symptoms of overdosage are involuntary movements, confusion, insomnia and more rarely—nausea, vomiting or cardiac arrhythmias. To treat overdosage, prompt evacuation of the stomach is recommended, as well as ECG monitoring of respiratory and heart function; it may be necessary to administer respiratory stimulants and/or antiarrhythmics, or, where appropriate, neuroleptics.

**Stability**

This medicine should not be used after the expiry date (EXP) shown on the pack.

**Drug Interactions**

Madopar may potentiate the effect of sympathomimetics given concomitantly. Close surveillance of the cardiovascular system is thus essential, and the dose of the sympathomimetic agents may need to be reduced. Because of the possibility of an additive effect when Madopar is used concurrently with antihypertensive agents, blood pressure must be regularly monitored in such cases. Neuroleptic drugs act as antagonists to the effects of Madopar. The effect of levodopa may be neutralized by vitamin B6. Such antagonism does not take place if
levodopa is combined with a decarboxylase inhibitor. Therefore, Madopar may be administered at the same time as multivitamin preparations containing vitamin B6. Combination with other antiparkinsonian agents (anticholinergics, amantadine, dopamine agonists) is permissible, though this may intensify both the desired and the undesired effects.

**Dosage and Administration**

**Standard Dosage**
Treatment with Madopar, as is usual for any levodopa therapy, should be introduced gradually; moreover, at all stages of the disease, dosage should be assessed individually and kept as low as possible. The following dosage instructions should therefore be regarded as guidelines.

When taking Madopar capsules, patients must always ensure that they swallow the capsule without chewing it. Madopar tablets, however, may be broken down into small pieces to facilitate swallowing. Madopar should be taken during meals or with sufficient food or liquid.

**Initial Therapy**
In the early stages of Parkinson's disease it is advisable to start treatment with 1 capsule of Madopar ‘62.5’ or ½ tablet of Madopar ‘125’ three or four times daily. Patients at a more advanced stage of the disease should receive twice as much. As soon as tolerability of the initial therapeutic schedule is confirmed, the dosage should be increased on a weekly basis by a single dose more per day (e.g. four daily doses instead of three, e.g.). If close supervision of the patient is possible, dosage adaptation may be made every two to three days. The optimal effect is generally reached at a daily dosage of 400-800 mg levodopa +100-200 mg benserazide, to be divided into three or more doses. If it proves necessary to further increase the daily dosage, this should be done on a monthly basis. Between four and six weeks may be needed to achieve the optimal dosage.

**Maintenance Therapy**
The average maintenance dosage is 1 capsule or 1 tablet of Madopar ‘125’ four to six times daily. The number of individual doses (not less than three) and their distribution throughout the day must be adapted to individual requirements.

**Special Dosage Instructions**
Non-levodopa-based antiparkinsonian agents can continue to be given until the full effects of Madopar are reached; after onset of the effect, however, they can often be gradually reduced. For patients who experience large fluctuations in the drug's effect during the course of the day (on-off phenomena) either more frequent and accordingly smaller single doses may need to be given. Dosage must be carefully titrated in every individual, including in elderly patients.