AUSTRALIAN PRODUCT INFORMATION
Madopar (levodopa and benserazide hydrochloride)

1. NAME OF THE MEDICINE
Levodopa and benserazide hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Madopar 62.5 capsule contains 50 mg Levodopa and 14.25 mg Benserazide (equivalent to 12.5 mg of the base)

Each Madopar 125 capsule contains 100 mg Levodopa and 28.5 mg Benserazide (equivalent to 25 mg of the base)

Each Madopar 250 capsule contains 200 mg Levodopa and 57 mg Benserazide (equivalent to 50 mg of the base)

Each Madopar HBS 125 capsule contains 100 mg Levodopa and 28.5 mg Benserazide (equivalent to 25 mg of the base)

Each Madopar 125 tablet contains 100 mg Levodopa and 28.5 mg Benserazide (equivalent to 25 mg of the base)

Each Madopar 250 tablet contains 200 mg Levodopa and 57 mg Benserazide (equivalent to 50 mg of the base)

Each Madopar Rapid 62.5 dispersible tablet contains 50 mg Levodopa and 14.25 mg Benserazide (equivalent to 12.5 mg of the base)

Each Madopar Rapid 125 dispersible tablet contains 100 mg Levodopa and 28.5 mg Benserazide (equivalent to 25 mg of the base)

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Madopar 62.5 capsules have a light grey opaque body with powder blue opaque cap, imprinted with 'ROCHE' on both ends

Madopar 125 capsules have a flesh coloured opaque body and powder blue opaque cap, imprinted with 'ROCHE' on both ends

Madopar 250 capsules have a caramel coloured opaque body and powder-blue opaque cap, imprinted with 'ROCHE' on both ends

Madopar HBS (Hydrodynamically Balanced System) 125 capsules have a light blue opaque body and dark green opaque cap imprinted with ‘ROCHE’ in red ink on both ends

Madopar 125 tablets are cylindrical, biconvex, pale red tablets, cross-scored on both sides

Madopar 250 tablets are cylindrical, biconvex, pale red tablets, imprinted with ‘ROCHE’ and a hexagon on one side, cross-scored on both sides

Madopar Rapid 62.5 dispersible tablets are off-white, cylindrical, bi-planar tablets with bevelled edges, imprinted with ‘ROCHE 62.5’ on one side and a break-bar on the other

Madopar Rapid 125 dispersible tablets are off-white, cylindrical, bi-planar tablets with bevelled edges, imprinted with 'ROCHE 125' on one side and a break-bar on the other

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Parkinson's disease and parkinsonian symptoms including post-encephalitic and toxic forms, but excluding drug induced parkinsonism.

Madopar HBS is indicated for patients presenting with all types of fluctuations in response (i.e. "peak dose dyskinesia" and "end of dose deterioration") and for better control of nocturnal symptoms.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

In order to reduce the incidence of adverse reactions and achieve maximal benefit, Madopar therapy must be individualised and drug administration must be continuously matched to the patient's needs and tolerance. Dosage must be carefully titrated in the elderly. Combined therapy with Madopar has a narrower therapeutic range than with levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and the dosage ranges recommended should usually not be exceeded. The appearance of involuntary movements should be regarded as a sign of levodopa toxicity and as an indication of overdosage requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesias.

The following schemes may be taken as a guide.

Initial treatment

The initial dosage schedule recommended is 1 capsule, tablet Madopar 125 or 125mg dispersible tablet three times daily. The daily dosage is then increased by 1 capsule, tablet Madopar 125 or 125mg dispersible tablet at weekly intervals until the individual therapeutic dosage is reached; when the patient can be followed very frequently the rate of dosage increase can be faster, e.g. twice a week. Thus the effective dose may be reached in as little as four days.

The effective dosage is generally between 4 and 8 capsules, tablets Madopar 125 or 125mg dispersible tablets daily, divided into three or four doses; it is rarely necessary to administer more than 10 capsules, tablets Madopar 125 or 125mg dispersible tablets daily.

Maintenance treatment

Madopar capsules or tablets can be used if the optimum therapeutic dosage amounts to more than 5 capsules or, tablets Madopar 125 or 125mg dispersible tablets daily, since it is advisable to divide the daily dosage into at least three doses.

The average maintenance dosage is 1 capsule or tablet Madopar three times daily, however, since the improvement may fluctuate, division of the daily dosage (regarding both the number of individual doses and their distribution through the day) must be adapted to individual requirements. If a patient begins to experience marked fluctuations in response in the course of the day (e.g. 'on-off' phenomena) the situation can often be noticeably improved by using Madopar 62.5, or, preferably by using Madopar HBS as recommended below.

If using Madopar 62.5 capsules or Madopar Rapid 62.5 tablets the total daily dosage is in principle not changed, but some (or all, if necessary) of the capsules or dispersible tablets of Madopar 125 or Madopar are replaced by capsules or dispersible tablets of Madopar 62.5, taken at shorter intervals.

Use of Madopar HBS

The switch to Madopar HBS is preferably made from one day to the next while keeping the same daily dose and the same frequency of intake. After two to three days, the dosage should be gradually increased by about 50%, because of the lower bioavailability of this special dosage form. Patients should be informed that their condition may deteriorate for a while.

Due to the pharmacokinetic properties of Madopar HBS, the onset of action is approximately three hours. If desired, effective plasma levels may be achieved more rapidly by administering Madopar HBS together with conventional capsules or 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 case of poor response to Madopar HBS even at daily doses corresponding to 1500mg of levodopa, or after six weeks treatment it is preferable to resume the previous treatment with the conventional capsules, tablets or dispersible tablets.

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

In patients with nocturnal disability, positive effects have been reported after gradually increasing the last evening dose up to three Madopar HBS capsules at bedtime. Patients should be carefully observed for possible psychic side effects.

Dosage must be carefully titrated in every individual, including in elderly patients.

Use of Madopar Rapid

Madopar Rapid 62.5 and Rapid 125 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 in patients who exhibit “delayed on” or “wearing off” phenomenon.

Conversion from levodopa alone to Madopar
Gradually reduce the dosage of levodopa until parkinsonian symptoms reappear or become marked; when this point has been reached replace each 500mg levodopa then being administered by 1 capsule, tablet Madopar 125 or 125mg dispersible tablet, since the efficacy of 1 capsule, tablet Madopar 125 or 125mg dispersible tablet is approximately equal to that of 500mg levodopa.

Observe the patient closely for one week, and then if necessary, begin to increase the dosage of Madopar until a satisfactory improvement is obtained (the dosage schedule is identical with that for patients not previously treated with levodopa); this dosage increase can be commenced earlier if there is a deterioration in the patient's clinical condition.

General remarks
In the rare cases in which intolerable side effects occur during the initial phase of treatment, incrementation of the dosage is stopped, or dosage is reduced. Withdrawal of the drug is seldom necessary. Once the side effects disappear or become tolerable, the daily dosage is again increased but more slowly, e.g. by 1 capsule, tablet Madopar 125 or 125mg dispersible tablet every two or three weeks.

The interval between dosage increases is longer when the average dosage (6 capsules, tablets Madopar 125 or 125mg dispersible tablets) has been exceeded, because a long period of time may elapse before the full effect of the product is observed.

Special populations
Renal impairment
No dose reduction is considered necessary in case of mild or moderate renal insufficiency (see section 4.3 Contraindications).

Hepatic impairment
The safety and efficacy of Madopar have not been established in patients with hepatic impairment (see section 4.3 Contraindications).

Method of Administration
Madopar capsules must always be swallowed whole. They must never be opened or dissolved in fluid.

Madopar tablets can be broken across the score line. Tablets which break incorrectly (i.e. away from the score line) should be discarded.

Madopar Rapid 62.5 and Rapid 125 tablets should be dispersed in a quarter of a glass of water (approx. 25-50 mL). The tablets completely disperse within a few minutes to give a milky white dispersion. Due to rapid sedimentation, it is advisable to stir the dispersion immediately before drinking. Madopar Rapid 62.5 and Rapid 125 tablets should be taken within half an hour of dispersing the tablets.

Where possible, Madopar should be taken either at least 30 minutes before or 1 hour after meals, so that the competitive effect of dietary protein on levodopa uptake can be avoided and

to facilitate a more rapid onset of action. However some patients find that Madopar is better tolerated if it is taken with food.

Like all replacement therapy, treatment with Madopar is permanent. Therapy with Madopar should be continued for at least six months before it is presumed to be ineffective.

The above dosage recommendations are based on the capsule dosage forms. However, the same doses may be achieved using the tablets which are cross-scored to facilitate titration of the dose to suit the patient's individual requirements.

4.3 CONTRAINDICATIONS

As with levodopa, patients in whom sympathomimetic amines are contraindicated should not receive Madopar. Monoamine oxidase inhibitors should not be given concomitantly and should be withdrawn at least two weeks prior to initiating Madopar therapy.

Madopar must not be given in conjunction with non-selective monoamine oxidase (MAO) inhibitors due to the risk of hypertensive crisis (see section 4.5 Interactions with other Medicines and other forms of Interaction). However, selective monoamine oxidase B (MAO-B) inhibitors, such as selegiline and rasagiline, and selective monoamine oxidase A (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 they should not be given concomitantly with Madopar.

Madopar should not be administered to patients with clinical or laboratory evidence of uncompensated cardiovascular, endocrine, renal, hepatic, haematological or pulmonary disease, or in patients with narrow angle glaucoma, or with active psychosis or serious psychoneurosis. Because levodopa may activate a malignant melanoma, Madopar should not be used in patients with suspicious, undiagnosed lesions or a history of melanoma. Madopar is contraindicated in the management of intention tremor and Huntington’s chorea.

Madopar must not be given to patients under 30 years of age.

Madopar is contraindicated in those patients who may be hypersensitive to levodopa, benserazide or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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

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 considerable incidence of subclinical osteoporosis and osteomalacia. In animal studies in rats, skeletal abnormalities resulting from disturbance of the growth of the epiphyseal plates, prior to closure, have occurred.

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.

Use in Patients with Wide-Angle Glaucoma
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.

Psychoactive Drugs
If concomitant administration of psychoactive drugs are necessary, they should be administered with great caution. Patients should be carefully observed for unusual, untoward drug effect (see section 4.3 Contraindications). Phenothiazines and butyrophenone derivatives may antagonise Madopar and in general should not be used.

Anaesthesia
If general anaesthesia is required, Madopar should, if possible be discontinued 2 or 3 days beforehand. On resumption of medication the dosage should be gradually stepped up again to the pre-operative level. Anaesthesia with cyclopropane or halothane should be avoided in emergency surgery. The patient must be closely supervised during the operation.

Somnolence
Madopar has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Madopar (see section 4.7 Effects on the Ability to Drive and Use Machinery). A reduction of dosage or termination of therapy may be considered.

Dopaminergic Drugs
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 drug. Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences.

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

Potential for Drug Dependence or Abuse
Dopamine dysregulation syndrome (DDS): a small number of patients 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.

Effect on Laboratory Tests
Madopar therapy may increase urinary catecholamines and metabolites and may therefore interfere with interpretation of urinary assays, e.g. diagnosis of adrenal tumours. False positive urine test results for ketone bodies have been reported.
Coombs' test may give false positive results in patients on Madopar therapy.

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

Uric acid, creatinine and glucose estimation may be interfered with by levodopa.

For reported biochemical disturbances see section 4.8 Adverse effects (Undesirable effects).

Use in the Elderly
No data available

Paediatric use
Madopar is contraindicated in patients less than 30 years old (see section 4.3 Contraindications)

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cardiovascular drugs: 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 effect of Madopar is not impaired by multivitamin preparations containing vitamin B_6

The absorption of levodopa from the gastrointestinal tract may be impaired by a protein-rich meal taken at the same time.

Pharmacokinetic Interactions
Coadministration of antacids with Madopar HBS reduces the extent of levodopa absorption by 32%. The HBS formulation showed a different pharmacokinetic profile when compared with Madopar when they were given with antacids. The rate of absorption of HBS was reduced and peak levels were lower. There was a tendency to produce a plateau, which lasted 2-4 hours, as the drug was being absorbed and eliminated at the same rate.

Ferrous sulphate decreases the maximum plasma concentration and the AUC of levodopa by 30-50%. This difference may result in a reduction of the effectiveness of Madopar.

Metoclopramide may increase the rate of levodopa absorption. The effect on the HBS formulation has not been examined.

Coadministration of domperidone with levodopa significantly increased the bioavailability of levodopa compared to levodopa given alone. Domperidone significantly increased the maximum plasma concentration of levodopa and the AUC from 0-3 hours by 1.5-fold and 1.3-fold respectively. Domperidone may increase the bioavailability of levodopa by stimulation of gastric emptying.

Pharmacodynamic Interactions
The action of Madopar is inhibited by neuroleptics and opioids.

Madopar should not be administered concomitantly with irreversible non-selective MAO inhibitors; there should be an interval of at least two weeks between stopping the MAO inhibitor and starting Madopar therapy. Otherwise unwanted side effects such as hypertensive crises are likely to occur. However, selective MAO-B inhibitors, such as selegiline, rasagiline and selective MAO-A inhibitors, such as moclobemide can be prescribed to patients on Madopar therapy and it may be necessary to adjust the patient's levodopa dose.

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 section 4.3 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 is necessary, monitoring of the cardiovascular system is essential, and the dose of the sympathomimetic agent may need to be reduced.

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 initiated.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy - Category B3
Madopar should not be taken during pregnancy or by women of childbearing potential in the absence of adequate contraception because of possible damage to foetal skeletal development.

Use in lactation
Madopar should not be given to nursing mothers as levodopa and benserazide may appear in the mother's milk; furthermore, levodopa may inhibit lactation and there is a possibility that the skeletal changes found in rats may be relevant to growing bones in humans.

Effects on Fertility
No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Madopar may have a major influence on the 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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. Mania, confusion and fainting have also been reported. Dopamine dysregulation syndrome (DDS) has been reported.

Nervous system disorders: abnormal involuntary movements (lips, head, tongue, cheeks, extremities), dyskinesia, hyperkinesia and involuntary jerks (muscle twitch and blepharospasm may be taken as early signs to consider dosage reduction), hiccups, nocturnal excitation, diurnal excitation, dizziness. Isolated cases of ageusia or dysgeusia have been reported. At later stages of the treatment, dyskinesia (e.g. choreiform or athetotic) may occur. With prolonged treatment, fluctuations in therapeutic response may also be encountered. They include freezing episodes, end-of-dose deterioration and the "on-off" effect. Madopar is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Cardiac disorders: cardiac arrhythmias, palpitations and angina pectoris have also been reported.

Respiratory disorders: dyspnoea.

Vascular disorders: orthostatic hypotension may occur occasionally. Orthostatic disorders commonly improve following reduction of the Madopar dosage.

Gastrointestinal disorders: nausea and vomiting (although these occur significantly less often with Madopar than with levodopa alone) and diarrhoea, sialorrhoea and constipation have been reported with Madopar.

Skin and subcutaneous tissue disorders: allergic skin reactions such as pruritus and rash may occur in rare cases.

Musculoskeletal disorders: muscle cramps, hypotonia, leg pain, torsion dystonia.

Reproductive disorders (male and female): changes in libido.

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

Investigations: 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. Serum protein-bound-iodine (PBI) levels may rise. Transient rise in bromsulphalein (BSP) retention. Prothrombin levels may rise. Transient fall in platelet and eosinophil count may occur. Urine may be altered in colour, usually red tinged and turns dark on standing. Other body fluids or tissues may also be discoloured or stained including saliva, the tongue, teeth or oral mucosa.

Post-Marketing

Blood and lymphatic system disorders: haemolytic anaemia, transient leukopenia and thrombocytopenia have been reported in rare cases. Therefore, as in any long-term levodopa-

containing treatment, blood cell count and liver and kidney function should be monitored periodically.

Metabolic and nutritional disorders: anorexia has been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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), gastrointestinal effects (e.g. nausea and vomiting) and abnormal involuntary movements.

If a patient has taken an overdose of a controlled release form of Madopar (e.g. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of Action
Levodopa is the metabolic precursor of dopamine. The latter is severely depleted in the striatum pallidum and substantia nigra of Parkinsonian patients and it is considered that the administration of levodopa raises the level of available dopamine in these centres. The major portion of a levodopa dose, however, is decarboxylated in tissues outside the brain. As a consequence the full therapeutic effect may not be obtained and side effects may occur.

The decarboxylase inhibitor, benserazide, at the recommended therapeutic dose does not cross the blood-brain barrier to any significant degree, although at very high doses it may enter the central nervous system.

Administration of benserazide makes it possible to inhibit the peripheral decarboxylation of levodopa without significantly affecting its metabolism in the brain. Combined therapy with

levodopa and benserazide reduces the amount of levodopa required for optimal therapeutic benefit and permits an earlier response to therapy.

The HBS form (Hydrodynamically Balanced System) provides prolonged release of the active ingredients in the stomach where the capsule remains for several hours. It ensures therapeutic levodopa plasma levels for several hours and a significant reduction of the concentration peaks.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Direct methods to measure benserazide are lacking, however, studies using radiolabelled benserazide have shown that 70% of the oral dose is absorbed from the intestine reaching peak plasma levels in about an hour. Measurements of the total radioactivity of the plasma levels indicate at least two metabolites with different half- lives. The metabolites in humans have not been clearly identified but probably include serine and trihydroxy-benzyl-hydrazine.

After a single oral dose of benserazide alone about 60% of the total radioactivity appears in the urine, most of it (85%) during the first 12 hours. 30% of the dose appears in the faeces. The presence of levodopa causes a somewhat higher absorption and excretion of the benserazide.

Levodopa is almost completely absorbed from conventional Madopar tablets and capsules giving peak levels in 1-2 hours. In the presence of benserazide the levels reached by 200 mg levodopa approximate those of 1000 mg levodopa alone. The duration of action of a dose of levodopa is variable according to the stage of the disease. 78% is excreted in the urine in 48 hours, with only about 0.2% in the faeces. Metabolites include homovanillic acid (24%) and mandelic acid.

The pharmacokinetic profile of levodopa following administration of Madopar Rapid is very similar to that following Madopar Standard in healthy volunteers and in Parkinsonian patients, but the time to peak concentrations tends to be shorter after Madopar Rapid.

The pharmacokinetic properties of the Madopar HBS form differ from those of the conventional capsules and tablets. The active ingredients are released slowly in the stomach. The maximum plasma concentration, which is lower than for the standard dosage forms, is reached approximately 3 hours after ingestion. The plasma concentration curve shows a longer "half-duration" (time span where plasma concentrations are equal to or higher than the half maximum concentration) than that of the conventional forms which indicates pronounced controlled-release properties.

The bioavailability of Madopar HBS is about 60% of the conventional capsules or tablets. The bioavailability is reduced by antacids but not by food.

5.3 PRECLINICAL SAFETY DATA

Genotoxity

No data available

Carcinogenicity

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Madopar125 and Madopar 250 Tablets

Mannitol
Microcrystalline cellulose
Crospovidone
Magnesium stearate
Pregelatinised maize starch
Ethylcellulose
Anhydrous calcium hydrogen phosphate
Colloidal anhydrous silica
Docusate sodium
Iron oxide red

Madopar Rapid 62.5 and Madopar Rapid 125 Tablets

Citric acid
Starch- maize
Microcrystalline cellulose
Magnesium stearate

Madopar 62.5, *Madopar 125 and Madopar 250* Capsules

Microcrystalline cellulose
Talc
Povidone
Magnesium stearate
Indigo carmine
Titanium dioxide
Iron oxide (red, yellow or black)
Gelatin
Madopar 62.5 capsules also contains mannitol.

Madopar HBS (Hydrodynamically Balanced System) Capsules:

Mannitol
Talc
Povidone
Magnesium stearate
Calcium hydrogen phosphate
Hypromellose
Hydrogenated vegetable oil

Indigo carmine
Iron oxide yellow
Titanium dioxide
Gelatin
TEKPRINT SW-1102 Red Ink used as a printing ink

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Madopar 62.5, 125, 250 capsules
Store below 30°C. Keep the bottle tightly closed.

Madopar HBS 125 capsules
Store below 30°C. Keep the bottle tightly closed.

Madopar 125 tablets
Store below 30°C. Keep the bottle tightly closed.

Madopar 250 tablets
Store below 25°C. Keep the bottle tightly closed.

Madopar Rapid 62.5 tablets
Store below 25°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Madopar 62.5, Madopar 125 and Madopar 250 capsules are supplied in amber glass bottles with HDPE cap with integral desiccant (bottle contains 100 capsules).

Madopar HBS 125 capsules are supplied in amber glass bottles with HDPE cap with integral desiccant (bottle contains 100 capsules).

Madopar 125 and Madopar 250 tablets are supplied in amber glass bottles with HDPE cap with integral desiccant (bottle contains 100 tablets).

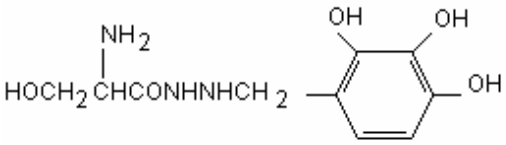
MADAPOR Rapid 62.5 and Madopar Rapid 125 dispersible tablets are supplied in amber glass bottles with HDPE cap with integral desiccant (bottle contains 100 tablets).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

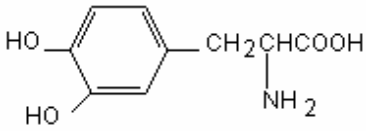
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



BENSERAZIDE



LEVODOPA

CAS number

Benserazide: 322 35 0

Levodopa: 59 92 7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine- S4

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

23 August 1991

10. DATE OF REVISION

8 July 2019

Summary table of changes

Section Changed	Summary of new information
All	New format and mandatory sections
8	Update to Sponsor address