NEW ZEALAND DATA SHEET
Madopar (Levodopa + benserazide)

1. PRODUCT NAME
Madopar 62.5 mg capsule

Madopar 125 mg capsule

Madopar 250 mg capsule

Madopar HBS 125 mg Modified release capsule

Madopar Rapid 62.5 mg Dispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 62.5 capsule contains 50 mg levodopa and 14.25 mg benserazide hydrochloride (equivalent to 12.5 mg of the base).

Each 125 capsule contains 100 mg levodopa and 28.5 mg benserazide hydrochloride (equivalent to 25 mg of the base).

Each 250 capsule contains 200 mg levodopa and 57 mg benserazide hydrochloride (equivalent to 50 mg of the base).

Each Madopar HBS 125 capsule contains 100 mg levodopa and 28.5 mg benserazide hydrochloride (equivalent to 25 mg of the base).

Each Madopar Rapid 62.5 dispersible tablet contains 50 mg levodopa and 14.25 mg benserazide hydrochloride (equivalent to 12.5 mg of the base).

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

3. PHARMACEUTICAL FORM
Madopar 62.5 capsule, a No. 4 size capsule with a “ROCHE” imprint, an opaque light-grey body and an opaque powder-blue cap.

Madopar 125 capsule, a No. 2 size capsule with a “ROCHE” imprint, an opaque flesh coloured body and an opaque powder-blue cap.

Madopar 250 capsule, a No. 1 size capsule with a “ROCHE” imprint, an opaque caramel coloured body and an opaque powder-blue cap.

Madopar 62.5 rapid dispersible tablet is an off-white, cylindrical, bi planar tablet with “ROCHE” and “62.5” imprinted on one side and a breakbar on the other side.

Madopar HBS 125 capsule (Hydrodynamically Balanced System with controlled release), a No. 1 size capsule with a “ROCHE” imprint, an opaque light blue body and an opaque dark green cap.

Madopar HBS 125 capsules must not be opened before ingestion because the controlled-release characteristics will be lost.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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.

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

Further experience is required to determine whether it is also advantageous to use Madopar HBS in new Parkinson patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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 Parkinson’s disease, it is advisable to start treatment with one capsule of Madopar 62.5 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 of 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 of Madopar 125 three to six 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 all patients (see section 4.1 Therapeutic Indications). 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 medication may need to be reduced or these medicines 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. in patients suffering from early morning and afternoon akinesia, or who exhibit “delayed on” or “wearing off” phenomena.

Patients who experience large fluctuations in the medicine’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 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.

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

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

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.

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 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.

4.3 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 (see section 4.4 Special warnings and precautions for use). 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 4.5 Interactions with other medicines and other forms of interactions).
- patients with decompensated endocrine, renal or hepatic function, cardiac disorders, psychiatric diseases with a psychotic component or closed angle glaucoma. Because levodopa may activate a malignant melanoma, Madopar should not be used in patients with suspicious, undiagnosed lesions or a history of melanoma.
- the management of patients with intention tremor and Huntington's chorea.
- patients less than 30 years old (skeletal development must be complete).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Hypersensitivity reactions may occur in susceptible individuals.

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

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

If a patient on levodopa requires a general anaesthetic, the normal Madopar regimen should be continued as close to the surgery as possible, except in the case of halothane. In general anaesthesia with halothane, Madopar 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.

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, hospitalised and rapid and appropriate

symptomatic treatment given. This may include resumption of Madopar therapy after an appropriate evaluation.

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 4.7 Effects on ability to drive and use machines).

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.

Dopaminergic medicines
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Madopar. Review of treatment is recommended if such symptoms develop. 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.

Potential for Medicine 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.

Effect on 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 anti-diabetic agents should be adjusted to blood sugar levels.

Levodopa may affect the results of laboratory tests for catecholamines, creatinine, uric acid and glucose. False positive urine tests for ketone bodies have been reported.

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

Use in Special Populations

<u>Renal impairment</u>
Levodopa and benserazide are both extensively metabolised 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 data with levodopa in renal impaired patients are not available. Madopar is well tolerated by uraemic patients undergoing haemodialysis.

Hepatic impairment
Levodopa is mainly metabolised by the aromatic amino acid decarboxylase that is abundantly present in the intestinal tract, in the kidney and heart in addition to the liver.
Pharmacokinetic data with levodopa in hepatic impaired patients are not 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

Pharmacokinetic interactions
Co-administration of the anticholinergic agent 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.
Co-administration 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 by stimulation of gastric emptying.

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 section 4.3 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 4.3 Contraindications).

Madopar should not be administered concomitantly with sympathomimetics (agents such as adrenaline, noradrenaline, 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, bromocripttine 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.

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

Concomitant administration of antipsychotics with dopamine-receptor blocking properties, particularly D2-receptor antagonists might antagonise the antiparkinsonian effects of levodopa-benserazide. Levodopa may reduce antipsychotic effects of these 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 anaesthetics (see section 4.4 Special warnings and precautions for use – General).

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy – Category B3

Madopar is contraindicated during pregnancy and in women of childbearing potential in the absence of adequate contraception. If pregnancy occurs in a woman taking Madopar, the medicine must be discontinued (as advised by the prescribing physician).

Breast-feeding

The safe use of Madopar during lactation has not been established. 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 cannot be excluded.

Fertility

No data available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 (see section 4.4 Special warnings and precautions for use - General).

4.8 UNDESIRABLE EFFECTS

Post marketing experience

The following adverse reactions have been identified from post marketing 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 (≥1/1,000 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	not known

- “on-off” effect	
Augmentation of RLS	not known
Somnolence	not known
Excessive daytime ~~somnolence~~ 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 4.4 Special warnings and precautions for use, *Effect on Laboratory Tests*

Description of selected adverse reactions

Blood and Lymphatic System Disorders

Haemolytic anaemia, transient leucopenia 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.

Central and Peripheral Nervous System Disorders
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 somnolence and sudden sleep onset episodes.

Musculoskeletal disorders
Muscle cramps, hypotonia

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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), gastro-intestinal effects (e.g. nausea and vomiting) and abnormal involuntary movements (see section 4.8 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 formulation further absorption should be prevented using an appropriate method.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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. Levodopa or L-DOPA (3,4-dihydroxy 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, it is metabolised 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.

Clinical trials
No text.

5.2 PHARMACOKINETIC 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 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 (hydrodynamically balanced system)
The pharmacokinetic properties of Madopar HBS differ from those of standard Madopar (capsules) 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 blood-brain barrier by a saturable transport system. It is not bound to plasma proteins, and its volume of distribution is 57 litres. The AUC of levodopa in cerebrospinal fluid is 12% of that in plasma.
In contrast to levodopa, benserazide does not penetrate the blood-brain barrier at therapeutic doses. It is concentrated mainly in the kidneys, lungs, small intestine and liver.

Metabolism
Levodopa is metabolised by two major pathways (decarboxylation and O-methylation) and two minor ones (transamination and oxidation).
Aromatic amino acid decarboxylase converts levodopa to dopamine. The major end-products of this pathway are homovanillic acid and dihydroxyphenylacetic acid. Catechol-O-methyltransferase methylates levodopa to 3-O-methyldopa. This major plasma metabolite has an elimination half-life of 15 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 (see

Pharmacokinetics in special populations). 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 faeces (24%).

Pharmacokinetics in special populations
No pharmacokinetic data are available in uraemic 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.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity
Carcinogenicity studies were not conducted with Madopar.

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

Impairment of fertility
No animal studies on fertility were performed with Madopar.

Teratogenicity
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 foetal weight decreased (rats).

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

No further animal data of relevance are available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

MADOPAR 62.5 capsules
Microcrystalline cellulose

Talc
Povidone
Magnesium stearate
Gelatin
Mannitol

Indigo carmine
Titanium dioxide and iron oxide (red, yellow or black)

MADOPAR 125 and 250 capsules
Microcrystalline cellulose
Talc
Povidone
Magnesium stearate
Gelatin
Indigo carmine
Titanium dioxide and iron oxide (red, yellow or black)

MADOPAR HBS (Hydrodynamically Balanced System) 125 capsules
Hypromellose
Hydrogenated vegetable oil
Calcium hydrogen phosphate
Mannitol
Povidone
Talc
Magnesium stearate
Gelatin
Indigo carmine
Titanium dioxide
Iron oxide
EKPRINT SW-1102 Red Ink.

MADOPAR Rapid 62.5 tablets
Citric acid
Maize starch
Microcrystalline cellulose
Magnesium stearate.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

All presentations

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

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

Madopar HBS 125 capsules

Store at or below 30°C. Keep the bottle tightly closed.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Roche Products (New Zealand) Limited

PO Box 109113

Newmarket, Auckland 1149

NEW ZEALAND

Medical enquiries: 0800 656 464

9. DATE OF FIRST APPROVAL

MADOPAR 62.5, 125, 250 capsules
19 August 1976

MADOPAR 62.5 Rapid tablets
16 March 1988

MADOPAR HBS 125 capsules
15 May 1989

10. DATE OF REVISION OF THE TEXT

11 March 2019

Summary of Changes Table

Section Changed	Summary of new information

All	New Data Sheet format, updated cross references and mandatory text
4.2, 4.3. 4.4, 4.8	Sections updated to align with Company Core Data Sheet, no change to overall information