SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Madopar 200 mg/50 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200.0mg Levodopa and 50mg Benserazide (as benserazide hydrochloride).

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules, hard

Light brown opaque body and a powder blue opaque cap, imprinted with the name

'Roche' in black ink on both sides

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Parkinsonism - idiopathic post-encephalitic

Previous neurosurgery is not a contra-indication to Madopar.

4.2 Posology and method of administration

Dosage and frequency of administration are variable and no more than a guide can be given.

Posology

Adults
Patients not previously treated with levodopa
The recommended initial dose is one capsule or dispersible tablet of Madopar 50 mg/12.5 mg three or four times daily. If the disease is at an advanced stage, the starting dose should be one capsule or dispersible tablet of Madopar 100 mg/25 mg three times daily.

The daily dosage should then be increased by one capsule or dispersible tablet of Madopar 100 mg/25 mg, or their equivalent, once or twice weekly until a full therapeutic effect is obtained, or side-effects supervene.

In some elderly patients, it may suffice to initiate treatment with one capsule or dispersible tablet of Madopar 50 mg/12.5 mg once or twice daily, increasing by one capsule or dispersible tablet every third or fourth day.

The effective dose usually lies within the range of four to eight capsules or dispersible tablets of Madopar 100 mg/25 mg (two to four capsules of Madopar 200 mg/50 mg) daily in divided doses, most patients requiring no more than six capsules or dispersible tablets of Madopar 100 mg/25 mg daily.

Optimal improvement is usually seen in one to three weeks but the full therapeutic effect of Madopar may not be apparent for some time. It is advisable, therefore, to allow several weeks to elapse before contemplating dosage increments above the average dose range. If satisfactory improvement is still not achieved, the dose of Madopar may be increased but with caution. It is rarely necessary to give more than ten capsules or dispersible tablets of Madopar 100 mg /25 mg (five capsules of Madopar 200 mg/50 mg) per day.

Treatment should be continued for at least six months before failure is concluded from the absence of a clinical response.

Madopar 50 mg/12.5 mg capsules or dispersible tablets may be used to facilitate adjustment of dosage to the needs of the individual patient. Patients who experience fluctuations in response may be helped by dividing the dosage into smaller, more frequent doses with the aid of Madopar 50 mg/12.5 mg capsules or dispersible tablets without, however, altering the total daily dose.

Madopar 200 mg/50 mg capsules are only for maintenance therapy once the optimal dosage has been determined using Madopar 100 mg/25 mg capsules or dispersible tablets.

Patients previously treated with levodopa

The following procedure is recommended: Levodopa alone should be discontinued and Madopar started on the following day. The patient should be initiated on a total of one less Madopar 100 mg/25 mg capsule or dispersible tablet daily than the total number of 500 mg levodopa tablets or capsules previously taken (for example, if the patient had previously taken 2g levodopa daily, then he should start on three capsules or dispersible tablets Madopar 100 mg/25 mg daily on the following day). Observe the patient for one week and then, if necessary, increase the dosage in the manner described for new patients.

Patients previously treated with other levodopa/decarboxylase inhibitor combinations

Previous therapy should be withdrawn for 12 hours. In order to minimise the potential for any effects of levodopa withdrawal, it may be beneficial to discontinue previous therapy at night and institute Madopar therapy the following morning. The initial Madopar dose should be one capsule or dispersible tablet of Madopar 50 mg/12.5 mg three or four times daily. This dose may then be increased in the manner described for patients not previously treated with levodopa.

Other anti-Parkinsonian drugs may be given with Madopar. Existing treatment with other anti-Parkinsonian drugs, e.g. anticholinergics or amantadine, should be continued during initiation of Madopar therapy. However, as treatment with Madopar proceeds and the therapeutic effect becomes apparent, the dosage of the other drugs may need to be reduced or the drugs gradually withdrawn.

Elderly
Although there may be an age-related decrease in tolerance to levodopa in the elderly, Madopar appears to be well-tolerated and side-effects are generally not troublesome.

Children
Not to be given to patients under 25 years of age: therefore, no dosage recommendations are made for the administration of Madopar to children.

Madopar capsules are for oral administration. They should be taken 30 min before or one hour after meals.

4.3 Contraindications

Madopar is contraindicated in:

-patients with known hypersensitivity to levodopa or benserazide or any of the excipients listed in section 6.1.

– patients receiving non-selective monoamine oxidase (MAO) inhibitors due to the risk of hypertensive crisis (see section 4.4). 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).

- patients with decompensated endocrine (e.g. phaeochromocytoma, hyperthyroidism, Cushing syndrome), renal or hepatic function, cardiac disorders (e.g. severe cardiac arrhythmias and cardiac failure), psychiatric diseases with a psychotic component or closed angle glaucoma (it may be used in wide-angle glaucoma provided that the intra-ocular pressure remains under control).

- patients less than 25 years old (skeletal development must be complete).

-pregnant women or to women of childbearing potential in the absence of adequate contraception. If pregnancy occurs in a woman taking Madopar, the drug must be discontinued (as advised by the prescribing physician).

Suspicion has arisen that levodopa may activate a malignant melanoma. Therefore, Madopar should not be used in persons who have a history of, or who may be suffering from, a malignant melanoma.

4.4 Special warnings and precautions for use

When other drugs must be given in conjunction with Madopar, the patient should be carefully observed for unusual side-effects or potentiating effects.

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.

Care should be taken when using Madopar in endocrine, renal, pulmonary or cardiovascular disease, particularly where there is a history of myocardial infarction or arrhythmia; psychiatric disturbances (e.g. depression); hepatic disorder; peptic ulcer; osteomalacia; where sympathomimetic drugs may be required (e.g. bronchial asthma), due to possible potentiation of the cardiovascular effects of levodopa; where antihypertensive drugs are being used, due to possible increased hypotensive action.

Care should be exercised when Madopar is administered to patients with pre-existing coronary artery disorders, cardiac arrhythmias or cardiac failure (see also section 4.3). Cardiac function should be monitored with particular care in such patients during the period of treatment initiation and regularly thereafter throughout treatment.

Close monitoring of patients with risk factors for (e.g. elderly patients, concomitant antihypertensives or other medication with orthostatic potential) or a history of orthostatic hypotension is recommended especially at the beginning of treatment or at dose increases.

Madopar has been reported to induce decreases in blood cell count (e.g. haemolytic anaemia, thrombocytopenia and leukopenia). In a few instances agranulocytosis and pancytopenia have been reported in which the association with Madopar could neither be established, nor be completely ruled out. Therefore, periodical evaluation of blood cell count should be performed during treatment.

Depression can be part of the clinical picture in patients with Parkinson’s disease and may also occur in patients treated with Madopar. All patients should be carefully monitored for psychological changes and depression with or without suicidal ideation.

Madopar may induce dopamine dysregulation syndrome resulting in excessive use of the product. A small subgroup of PD 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.

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, additional signs in severe cases may include myoglobinuria, rhabdomyolysis – and acute renal failure) 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.

Pyridoxine (vitamin B_6) may be given with Madopar since the presence of a decarboxylase inhibitor protects against the peripheral levodopa transformation facilitated by pyridoxine.

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).

Impulse control disorders

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.

Malignant melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 fold higher). It is unclear whether the increased risk observed was due to Parkinson's disease, or other factors such as levodopa used to treat Parkinson's disease. Therefore, patients and providers are advised to monitor for melanomas on a regular basis when using Madopar for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).

Warnings related to Interactions

If a patient 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.

If a patient has to undergo emergency surgery, when Madopar has not been withdrawn, anaesthesia with halothane should be avoided.

If levodopa-benserazide 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 levodopa-benserazide therapy. Otherwise unwanted effects such as hypertensive crisis are likely to occur (see section 4.3).

Concomitant administration of antipsychotics with dopamine-receptor blocking properties, particularly D2-receptor antagonists might antagonize the antiparkinsonian effects of levodopa-benserazide, therefore, should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect and worsening of parkinsonian symptoms.

Concomitant administration of levodopa-benserazide with sympathomimetics (agents such as epinephrine, norepinephrine, isoproterenol or amphetamine which stimulate the sympathetic nervous system) may potentiate their effects, therefore these combinations are not recommended. 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.

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

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

Combination with anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists are permissible, though both the desired and the undesired effects of treatment may be intensified. It may be necessary to reduce the dosage of levodopa-benserazide or the other substance.

Laboratory tests

Periodical evaluation of hepatic, haemopoietic, renal and cardiovascular function and blood 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.

Patients who improve on Madopar therapy should be advised to resume normal activities gradually as rapid mobilisation may increase the risk of injury.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Co-administration of the anticholinergic drug trihexyphenidyl with standard dosage form of Madopar reduces the rate, but not the extent, of levodopa absorption. Trihexyphenidyl given concomitantly with Madopar CR formulation does not affect the pharmacokinetics of levodopa.

Ferrous sulfate decreases the maximum plasma concentration and the AUC of levodopa by 30 - 50%. The pharmacokinetic changes observed during co-treatment with ferrous sulfate appeared to be clinically significant in some but not all patients.

Opioids and drugs which interfere with central amine mechanisms, such as rauwolfia alkaloids (reserpine), tetrabenazine (Nitoman), metoclopramide, phenothiazines, thioxanthenes, butyrophenones, amphetamines and papaverine, should be avoided where possible. If, however, their administration is considered essential, extreme care should be exercised and a close watch kept for any signs of potentiation, antagonism or other interactions and for unusual side-effects. 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

Concomitant administration of antipsychotics with dopamine-receptor blocking properties, particularly D2-receptor antagonists might antagonize the antiparkinsonian effects of Madopar, therefore, should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect and worsening of parkinsonian symptoms.

Symptomatic orthostatic hypotension occurred when combinations of levodopa and a decarboxylase inhibitor were added to the treatment of patients already receiving antihypertensives. Madopar needs to be introduced cautiously in patients receiving antihypertensive medication. Blood pressure needs to be monitored to allow for potential dosage adjustment of either of the drugs, if required.

Concomitant administration of Madopar with sympathomimetics (agents such as epinephrine, norepinephrine, isoproterenol or amphetamine which stimulate the sympathetic nervous system) may potentiate their effects, therefore these combinations are not recommended. 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.

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 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 levodopa-benserazide. 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 4.3 Contraindications).

Combination with anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists are permissible, though both the desired and 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.

Levodopa may affect the results of laboratory tests for catecholamines, ketone bodies, creatinine, uric acid and glycosuria. The urine test results may give a false positive for ketone bodies.

Levodopa therapy has been reported to inhibit the response to protirelin in tests of thyroid function.

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

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.

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: levodopa-benserazide 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 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Madopar is contra-indicated in pregnancy and in women of childbearing potential in the absence of adequate contraception (see section 4.3 and section 5.3).

A pregnancy test prior treatment is recommended to exclude pregnancy.

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

Labor and delivery

The safe use of levodopa-benserazide during labor and delivery has not been established.

Breast-feeding

The safe use of levodopa-benserazide during lactation has not been established.

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

Fertility

No fertility studies have been performed.

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 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).

4.8 Undesirable effects

The following undesirable effects have been identified from post marketing experience with Madopar. (*frequency not known, cannot be estimated from the available data*) based on spontaneous case reports and literature.

Frequency categories are as follows:

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 (cannot be estimated from the available data)

Blood and Lymphatic System Disorder	
frequency not known	Haemolytic anaemia
	Leukopenia
	Thrombocytopenia
Metabolic and nutritional disorders	
frequency not known	Decreased appetite
Psychiatric Disorders	
frequency not known	Dopamine dysregulation syndrome
	Confusional state
	Depression
	Agitation *
	Anxiety*
	Insomnia*
	Hallucination*
	Delusion*
	Disorientation*
	Pathological gambling
	Increased libido
	Hypersexuality
	Compulsive shopping
	Binge eating
	Eating disorder symptom
Nervous System Disorders	
frequency not known	Ageusia
	Dysgeusia
	Dyskinesia (choreiform and athetotic)
	Fluctuations in therapeutic response
	Freezing phenomenon
	End-of-dose deterioration

	On and off phenomenon
	Restless legs syndrome
	Somnolence
	Sudden onset of sleep
Cardiac disorders	
frequency not known	Arrhythmia
Vascular Disorders	
frequency not known	Orthostatic hypotension
Gastrointestinal disorders	
frequency not known	Nausea
	Vomiting
	Diarrhoea
	Saliva discolouration
	Tongue discolouration
	Tooth discolouration
	Oral mucosa discolouration
Liver and Biliary disorders	
frequency not known	Transaminases increased
	Alkaline phosphatase increased
	Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	
frequency not known	Pruritus
	Rash
Renal and urinary disorders	
frequency not known	Blood urea increased
	Chromaturia

*These events may occur particularly in elderly patients and in patients with a history of such disorders.

Impulse Control Disorders:

Impulse control disorders such as 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. (see section 4.4).

Nervous System Disorder:

Psychiatric disturbances are common in Parkinsonian patients, including those treated with levodopa, including mild elation, anxiety, agitation, insomnia, drowsiness, depression, aggression, delusions, hallucinations, temporal disorientation and "unmasking" of psychoses.

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. Levodopa-benserazide is associated with somnolence and has been associated very rarely with excessive daytime sleepiness and sudden sleep onset episodes.

Restless Legs Syndrome: The development of augmentation (time shift of symptoms from the evening/night into the early afternoon and evening before taking the next nightly dose, is the most common adverse effect of dopaminergic long-term treatment.

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.
- Gastro-intestinal bleeding has been reported with levodopa therapy.
- Isolated cases of loss or alterations of taste.

Vascular Disorders:

Orthostatic disorders commonly improve following reduction of the Madopar dosage.

Others:

Flushing and sweating have been reported with levodopa.

Investigations:

Urine may be altered in colour; usually acquiring a red-tinge which turns dark on standing. These changes are due to metabolites and are no cause for concern.

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 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 via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Symptoms of overdosage 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).

Management

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Madopar is an anti-Parkinsonian agent. 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 administration of levodopa raises the level of available dopamine in these centres. However, conversion of levodopa into dopamine by the enzyme dopa

decarboxylase also takes place in extracerebral tissues. As a consequence the full therapeutic effect may not be obtained and side-effects occur.

Administration of a peripheral decarboxylase inhibitor, which blocks the extracerebral decarboxylation of levodopa, in conjunction with levodopa has significant advantages; these include reduced gastro-intestinal side-effects, a more rapid response at the initiation of therapy and a simpler dosage regimen. Madopar is a combination of levodopa and benserazide in the ratio 4:1 which in clinical trials has been shown to be the most satisfactory.

Like every replacement therapy, chronic treatment with Madopar will be necessary.

5.2 Pharmacokinetic properties

Absorption

Low levels of endogenous levodopa are detectable in pre-dose blood samples. After oral administration of Madopar, levodopa and benserazide are rapidly absorbed, mainly in the upper regions of the small intestine and absorption there is independent of the site. Interaction studies indicate that a higher proportion of levodopa is absorbed when administered in combination with benserazide, compared with levodopa administered alone. Maximum plasma concentrations of levodopa are reached approximately one hour after ingestion of Madopar. The absolute bioavailability of levodopa from standard Madopar is approximately 98%.

The maximum plasma concentration of levodopa and the extent of absorption (AUC) increase proportionally with dose (50 – 200 mg levodopa). The peak levodopa plasma concentration is 30% lower and occurs later when Madopar is administered after a standard meal. Food intake generally reduces the extent of levodopa absorption by 15% but this can be variable.

Distribution

Levodopa crosses the gastric mucosa and the blood-brain barrier by a saturable transport system. It is not bound to plasma proteins. Benserazide does not cross the blood-brain barrier at therapeutic doses. Benserazide is concentrated mainly in the kidneys, lungs, small intestine and liver.

Biotranformation

The 2 major routes of metabolism of levodopa are decarboxylation to form dopamine, which in turn is converted to a minor degree to norepinephrine and to a greater extent, to inactive metabolites, and O-methylation, forming 3-O-methyldopa, which has an elimination half-life of approximately 15 hours and accumulates in patients receiving 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.

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 the peripheral decarboxylase inhibitor, benserazide, the elimination half-life of levodopa is approximately 1.5 hours. In elderly patients the elimination half-life is slightly (25%) longer. Clearance of levodopa is 430ml/min.

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

5.3 Preclinical safety data

See 4.6 Pregnancy and Lactation

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Microcrystalline cellulose (E460)
Povidone K90 (E1201)
Talc (E553b)
Magnesium stearate (E572)

Capsule shell:
Gelatin
Indigo carmine (E132)
Titanium dioxide (E171)
Iron oxide (E172)

Printing Ink:
Black iron oxide (E172)

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package. Keep bottle tightly closed.

6.5 Nature and contents of container

Amber glass bottles with polyethylene closure with integrated desiccant containing 100 capsules.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00031/0074R

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/07/1990

10 DATE OF REVISION OF THE TEXT

31/03/2020