SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Madopar CR 100 mg/25 mg Prolonged Release Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 100.0mg Levodopa and 25mg Benserazide (as benserazide hydrochloride)
For excipients see section 6.1

3 PHARMACEUTICAL FORM
Prolonged-release capsules, hard
Light blue opaque body and dark green opaque cap imprinted with ROCHE in red.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of all stages of Parkinson’s disease. Patients with fluctuations related to levodopa plasma concentrations or timing of dose, e.g. end of dose deterioration or wearing-off effects, are more likely to benefit from switching to Madopar CR.

4.2 Posology and method of administration
Adults, including the elderly
Dosage and administration are very variable and must be titrated to the needs of the individual patient.

Madopar CR capsules must always be swallowed whole, preferably with a little water. They may be taken with or without food but antacid preparations should be avoided.

In patients with nocturnal immobility, positive effects have been reported after gradually increasing the last evening dose to two Madopar CR 100mg/25mg capsules on retiring.

Patients not currently treated with levodopa
In patients with mild to moderate disease, the initial recommended dose is one capsule of Madopar CR three times daily with meals. Higher doses, in general, of Madopar CR will be required than with conventional levodopa-
decarboxylase inhibitor combinations as a result of the reduced bioavailability. The initial dosages should not exceed 600mg per day of levodopa.

Some patients may require a supplementary dose of conventional Madopar, or Madopar Dispersible, together with the first morning dose of Madopar CR to compensate for the more gradual onset of the CR formulation.

In cases of poor response to Madopar CR at total daily doses of Madopar CR plus any supplementary conventional Madopar corresponding to 1200mg levodopa, administration of Madopar CR should be discontinued and alternative therapy considered.

**Patients currently treated with levodopa**

Madopar CR should be substituted for the standard levodopa-decarboxylase inhibitor preparation by one capsule Madopar CR 100mg/25mg per 100mg levodopa. For example, where a patient previously received daily doses of 200mg levodopa with a decarboxylase inhibitor, then therapy should be initiated with two capsules Madopar CR 100mg/25mg. Therapy should continue with the same frequency of doses as previously.

With Madopar CR, on average, a 50% increase in daily levodopa dosage compared with previous therapy has been found to be appropriate. The dosage should be titrated every 2 to 3 days using dosage increments of Madopar CR 100mg/25mg capsules and a period of up to 4 weeks should be allowed for optimisation of dosage.

Patients already on levodopa therapy should be informed that their condition may deteriorate initially until the optimal dosage regimen has been found. Close medical supervision of the patient is advisable during the initial period whilst adjusting the dosage.

**Children**

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

### 4.3 Contraindications

Madopar must not be given to patients with known hypersensitivity to levodopa or benserazide or any of the excipients.

Madopar must not be given in conjunction with non-selective monoamine oxidase (MAO) inhibitors. 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).

Madopar must not be given to patients with decompensated endocrine (e.g. phaeochromocytoma, hyperthyroidism, Cushing syndrome), renal (except RLS patients on dialysis) 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).

Madopar must not be given to patients less than 25 years old (skeletal development must be complete).

Madopar must not be given to 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 the following circumstances: 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 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 count should be performed during treatment.
Depression can be part of the clinical picture in patients with Parkinson’s disease and RLS 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.

If a patient 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.

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

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 B6) 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.
**Laboratory tests**
Periodical evaluation of hepatic, haemopoietic, renal and cardiovascular function and blood count should be performed during treatment.

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

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

**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).

### 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 rauwolvia alkaloids (reserpine), tetrabenzaine (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 by stimulation of gastric emptying.

**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 crises 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 other anti-Parkinsonian agents such as 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 glucose. 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.

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
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).

Since it is not known whether benzerazide 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.

4.7 Effects on ability to drive and use machines

Patients being treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see Section 4.4).

4.8 Undesirable effects

The following undesirable effects have been reported (frequency not known, cannot be estimated from the available data) to occur when levodopa-benserazide is administered:

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)

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<th>Blood and Lymphatic System Disorder</th>
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<th>Decreased appetite</th>
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<th>Psychiatric Disorders</th>
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<tr>
<td>frequency not known</td>
<td>Confusional state</td>
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<td></td>
<td>Depression</td>
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<td>Agitation *</td>
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<td>Condition</td>
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<td>Disorientation*</td>
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<td>Pathological gambling</td>
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<td>Increased libido</td>
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<td>Hypersexuality</td>
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<td>Compulsive shopping</td>
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<td><strong>Nervous System Disorders</strong></td>
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<td>Dysgeusia</td>
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<td>Dyskinesia (choreiform and athetotic)</td>
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<td>Fluctuations in therapeutic response</td>
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<td>End-of-dose deterioration</td>
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<td>On and off phenomenon</td>
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<td>Somnolence</td>
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<td>Sudden onset of sleep</td>
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<td>Arrhythmia</td>
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<td><strong>Vascular Disorders</strong></td>
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<td>Orthostatic hypotension</td>
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<td><strong>Gastrointestinal disorders</strong></td>
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<tr>
<td>Nausea</td>
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<td>Vomiting</td>
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<td>Diarrhoea</td>
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<td>Saliva discolouration</td>
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<td>Tongue discolouration</td>
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<td>Tooth discolouration</td>
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<td>Oral mucosa discolouration</td>
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<td><strong>Liver and Biliary disorders</strong></td>
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<td>Transaminases increased</td>
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<td>Alkaline phosphatase increased</td>
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<td>Gamma-glutamyltransferase increased</td>
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<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<td>Pruritus</td>
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<td>Rash</td>
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<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<td>Restless legs syndrome</td>
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<td><strong>Renal and urinary disorders</strong></td>
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<td>Blood urea increased</td>
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<td>Chromaturia</td>
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*These events may occur particularly in elderly patients and in patients with a history of such disorders.

**Impulse Control Disorders:**
- 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 somnolence and sudden sleep onset episodes.

**Gastrointestinal disorders:**
- Undesirable gastrointestinal effects, which may occur mainly in the early stages of the treatment, can largely be controlled by taking Madopar with some food 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.

**Musculoskeletal and connective tissue disorders:**
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.

**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](http://www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

**Symptoms and signs**

Symptoms and signs 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).

If a patient has taken an overdose of Madopar CR, 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 Madopar CR further absorption should be prevented using an appropriate method.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

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 consists of levodopa and the peripheral decarboxylase inhibitor benserazide in the ratio 4:1 which in clinical trials has been shown to be the most satisfactory combination.
Like every replacement therapy, chronic treatment with Madopar will be necessary.

5.2 Pharmacokinetic properties
Madopar CR is a controlled-release form which provides more prolonged, but lower, peak plasma concentrations of levodopa than standard Madopar or other conventional formulations of levodopa.

Absorption
The active ingredients of Madopar CR are released slowly in the stomach and the maximum levodopa plasma concentration is reached approximately 3 hours after ingestion. The plasma concentration-time curve for levodopa shows a longer “half-duration” (= time-span when plasma concentrations are equal to or higher than half the maximum concentration) than that of standard Madopar, which indicates pronounced controlled-release properties. Madopar CR bioavailability is approximately 60% that of standard Madopar and is not affected by food. Maximum plasma concentrations of levodopa are not affected by food but occur later (five hours) after postprandial administration. Co-administration of an antacid with Madopar CR reduces the extent of levodopa absorption by 32%.

Distribution
Levodopa crosses 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.

Metabolism
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%).
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents:
- Hypromellose (E464)
- Hydrogenated vegetable oil
- Calcium hydrogen phosphate, anhydrous (E341)
- Mannitol (E421)
- Talc (E553b)
- Povidone (E1201)
- Magnesium stearate (E572)

Capsule shell:
- Gelatin
- Indigo carmine (E132)
- Titanium dioxide (E171)
- Yellow iron oxide (E172)

Printing ink:
- Red iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package. Keep bottle tightly closed.

6.5 Nature and contents of container
Amber glass bottles with polyethylene closure and 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 00031/0227

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/02/1989

10 DATE OF REVISION OF THE TEXT
10/03/2016