

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Madopar 200 mg/50 mg hard capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200.0 mg levodopa and 50 mg benserazide (as benserazide hydrochloride).

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsules, hard (Capsules)

Light brown, opaque body and a powder blue, opaque cap, imprinted with the name 'ROCHE' in black ink on both sections.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

In the management of Parkinsonism of idiopathic, post-encephalitic or arteriosclerotic type.

### 4.2 Posology and method of administration

#### Posology

#### ***Adults over the age of 25 years only:***

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

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

The daily dosage should then be increased by one dispersible tablet of Madopar 100mg/25mg, or the 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 dispersible tablet of Madopar 50mg/12.5mg once or twice daily, increasing by one capsule every third or fourth day.

The effective dose usually lies within the range of four to eight dispersible tablets of Madopar 100mg/25mg (two to four capsules of Madopar 200mg/50mg) daily in divided doses, most patients requiring no more than six dispersible tablets of Madopar 100mg/25mg 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 10 dispersible tablets of Madopar 100mg/25mg (five capsules of Madopar 200mg/50mg) per day.

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

Madopar 50mg/12.5mg 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 50mg/12.5mg dispersible tablets without, however, altering the total daily dose.

**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 100mg/25mg dispersible tablet daily than the total number of 500mg levodopa tablets or capsules previously taken (for example, if the patient had previously taken 2g levodopa daily, then he should start on three dispersible tablets of Madopar 100mg/25mg 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 dispersible tablet of Madopar 50mg/12.5mg 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**

Madopar is contraindicated in patients under 25 years of age, therefore no dosage recommendations are made for administration of Madopar capsules to children.

Method of Administration

Madopar capsules are for oral administration.

When taking Madopar capsules, patients must always ensure that they swallow the whole capsule without chewing it.

Where possible, Madopar should be taken in-between meals, so that the competitive effect of dietary protein on levodopa can be avoided (see Section 4.5) and to facilitate a more rapid onset of action. A delay between a meal and Madopar dosing may be advisable to avoid lower absorption of levodopa by food (see section 5.2). 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.

**4.3 Contraindications**

Madopar is contraindicated in:

- patients with a 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.* pheochromocytoma, hyperthyroidism, Cushing syndrome), renal (except RLS patients on dialysis) or hepatic function.

- patients with cardiac disorders (e.g. severe cardiac arrhythmias and cardiac failure).
- patients with psychiatric diseases with a psychotic component.
- patients with 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 (see Section 4.6). 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 (see "Warnings related to Interactions" and Section 4.5).

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 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 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.

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<sub>6</sub>) 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 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.

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).

Concomitant administration of antipsychotics with dopamine-receptor blocking properties, particularly D<sub>2</sub>-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.

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.

When initiating an adjuvant treatment with a catechol-O-methyltransferase (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.

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.

### Laboratory tests

Periodical evaluation of hepatic, haemopoietic, renal and cardiovascular function and blood cell count should be performed during treatment (see Section 4.8).

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 interactions**

### 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.

Ferrous sulfate decreases maximum plasma concentration and the AUC of levodopa by 30 – 50%. The pharmacokinetic changes observed during co-treatment with ferrous sulfate appear 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

Neuroleptics, opioids and antihypertensive medications containing reserpine inhibit the action of Madopar.

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 anticholinergics, amantadine, selegiline, bromocriptine and dopamine agonists are permissible, though both the desired and undesired effects of treatment may be intensified. 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 (see section 5.2). Levodopa is a large neutral amino acid (LNAA) and it competes with LNAAs from dietary protein for transport across the mucosa of the upper regions of the small intestine 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 anaesthesia 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).

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).

##### Breast-feeding

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

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 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 levodopa- benserazide (*frequency not known, cannot be estimated from the available data*) based on spontaneous case reports and literature cases:

Frequency categories are as follows:

Very common:  $\geq 1/10$ ;

Common  $\geq 1/100$  to  $< 1/10$ ;

Uncommon  $\geq 1/1,000$  to  $< 1/100$

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare (&lt;1/10,000)

Not known (cannot be estimated from the available data)

|                                               |                                             |
|-----------------------------------------------|---------------------------------------------|
| <b>Blood and Lymphatic System Disorder</b>    |                                             |
| frequency not known                           | Haemolytic anaemia                          |
|                                               | Leukopenia                                  |
|                                               | Thrombocytopenia                            |
| <b>Metabolic and nutritional disorders</b>    |                                             |
| frequency not known                           | Decreased appetite                          |
| <b>Psychiatric Disorders</b>                  |                                             |
| 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                       |                                             |
| <b>Nervous System Disorders</b>               |                                             |
| frequency not known                           | Ageusia                                     |
|                                               | Dysgeusia                                   |
|                                               | Dyskinesia (choreiform and athetotic)       |
|                                               | <i>Fluctuations in therapeutic response</i> |
|                                               | Freezing phenomenon                         |
|                                               | <i>End-of-dose deterioration</i>            |
|                                               | On and off phenomenon                       |
|                                               | Restless legs syndrome                      |
|                                               | Somnolence                                  |
|                                               | Sudden onset of sleep                       |
| <b>Cardiac disorders</b>                      |                                             |
| frequency not known                           | Arrhythmia                                  |
| <b>Vascular Disorders</b>                     |                                             |
| frequency not known                           | Orthostatic hypotension                     |
| <b>Gastrointestinal disorders</b>             |                                             |
| frequency not known                           | Nausea                                      |
|                                               | Vomiting                                    |
|                                               | Diarrhoea                                   |
|                                               | Saliva discolouration                       |
|                                               | Tongue discolouration                       |
|                                               | Tooth discolouration                        |
|                                               | Oral mucosa discolouration                  |
| <b>Liver and Biliary disorders</b>            |                                             |
| frequency not known                           | Transaminases increased                     |
|                                               | Alkaline phosphatase increased              |
|                                               | Gamma-glutamyltransferase increased         |
| <b>Skin and subcutaneous tissue disorders</b> |                                             |
| frequency not known                           | Pruritus                                    |
|                                               | Rash                                        |
| <b>Renal and urinary disorders</b>            |                                             |
| frequency not known                           | Blood urea increased                        |

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

**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 is no cause for concern.

Other body fluids or tissues may also be discoloured or stained including saliva, the tongue, teeth or oral mucosa.

Tolerance to Madopar varies widely between patients and is often related to the rate of dosage increases. With long-term administration, fluctuations in the therapeutic response may be encountered. They include "freezing" episodes, end-of-dose deterioration and the so-called "on-off" effect. Patients may be helped by dosage reduction or by giving smaller and more frequent doses.

**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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2. Tel: +353 1 6764971, Fax: +353 1 6762517.

Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).



## 4.9 Overdose

### Symptoms and signs

Symptoms and signs of overdosage are qualitatively similar to the side-effects of madopar 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).

### Treatment

Monitor the patients vital signs and institute supportive measures as indicated by the patients 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

Madopar is an anti-Parkinsonian agent. A combination of levodopa, the precursor of dopamine, the levels of which are reduced in Parkinsonism, and benserazide, a peripheral inhibitor of decarboxylase, in the ratio of 4:1. Benserazide permits higher levels of levodopa to reach the brain by decreasing the peripheral metabolism of the latter to dopamine, which cannot reach the brain.

### 5.2 Pharmacokinetic properties

#### **Absorption**

After oral administration, Madopar, levodopa and benserazide are mainly absorbed in the upper regions of the small intestine, and absorption there is independent of the site. Maximum plasma concentrations of levodopa are reached after approximately one hour after ingestion. 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 – 200mg levodopa).

Food intake reduces the rate and extent of levodopa absorption by approximately 30% and 15% respectively.

#### **Distribution**

Levodopa crosses the mucosa of the upper regions of the small intestine and 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 – methyl dopa, which has an elimination half-life of approx. 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 – methyl dopa.

Benserazide is hydroxylated to trihydroxylhydrazine in the intestinal mucosa and 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 (approx. 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 smaller extent in the faeces (24%).

### 5.3 Preclinical safety data

There are no available non-clinical data of relevance to the prescriber.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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

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 to protect from moisture.

### 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Roche Products (Ireland) Ltd  
3004 Lake Drive  
Citywest  
Naas Road  
Dublin 24  
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA2307/004/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

**10 DATE OF REVISION OF THE TEXT**

February 2021