

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0050/043/007**

Case No: 2050519

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Roche Products Ltd**

**6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Madopar CR 100mg/25mg Prolonged Release Hard Capsules**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **01/04/2009**.

Signed on behalf of the Irish Medicines Board this

\_\_\_\_\_

A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Madopar CR 100mg/25mg Prolonged Release Hard Capsules

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100.0 mg levodopa and 25 mg benserazide (as benserazide hydrochloride).

For a full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Prolonged release capsules, hard (Prolonged release Capsules)

Light blue opaque body and dark green opaque cap imprinted with 'Roche' in red.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

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

In particular in patients presenting with fluctuations in response to conventional levodopa preparations and alleviation of nocturnal symptoms and early morning akinesia.

##### 4.2 Posology and method of administration

###### *Adults, including the elderly*

Dosage depends upon titration based on the individual patient response.

In general higher doses will be required (on average a 50% increase in daily levodopa dosage) for the CR form than for the conventional form.

A supplementary dose of conventional product may be required.

###### *Nocturnal symptoms*

Initially one capsule of Madopar CR should be taken on retiring; this may be gradually increased to a maximum of three capsules taken as a single dose on retiring. The patients usual daytime therapy should be continued.

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 should be informed that their condition may deteriorate initially until the optimal dosage regimen has been found.

###### *Fluctuations in response to conventional therapy*

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 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 and a period of up to 4 weeks should be allowed for optimisation of 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 a known hypersensitivity to levodopa or benserazide.

Madopar is contra-indicated in narrow-angle glaucoma; severe psychoses, severe endocrine, renal, hepatic or cardiac disorders.

It should not be given in conjunction with, or within 2 weeks of withdrawal of, monoamine oxidase (MAO) inhibitors except selective MAO-B inhibitors (e.g. selegiline) or selective MAO-A inhibitors (e.g. moclobemide).

It should not be given to patients under 25 years of age.

It should 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.

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.

In the event of general anaesthesia being required, Madopar therapy may be continued as long as the patient is able to take fluids and medication by mouth. If therapy is temporarily interrupted, the usual daily dosage may be administered as soon as the patient is able to take oral medication. Whenever therapy has been interrupted for longer periods, dosage should again be adjusted gradually. However, in many cases the patient can rapidly be returned to his previous therapeutic dosage.

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

There have been occasional reports of a neuroleptic malignant-like syndrome, involving hyperthermia, on abrupt withdrawal of levodopa preparations. Sudden discontinuation of Madopar, without close supervision, or "drug holidays" should therefore be avoided.

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.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists and/or levodopa for Parkinson's disease.

*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.

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

Periodic evaluation of hepatic, haemopoietic, renal and cardiovascular function is advised.

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**

Ferrous sulphate decreases the maximum plasma concentration and the AUC of levodopa by 30 - 50%. The pharmacokinetic changes observed during co-treatment with ferrous sulphate 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 has been shown to increase the rate of levodopa absorption.

Combination with other anti-Parkinsonian agents (anticholinergics, amantadine, dopamine agonists) is 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.

Use with antihypertensive agents may increase the hypotensive response, while sympathomimetics may increase the cardiovascular side-effects of levodopa.

Levodopa may interfere chemically with several diagnostic laboratory tests including those for glucose, ketone bodies, or catecholamines in urine and for glucose or uric acid in blood. Levodopa therapy has been reported to inhibit the response to protirelin in tests of thyroid function.

When Madopar CR is given with antacid preparations the bioavailability of levodopa is reduced, in comparison with conventional Madopar.

## **4.6 Pregnancy and lactation**

Madopar is contra-indicated in pregnancy and in women of childbearing potential in the absence of adequate contraception, since there is evidence of harmful effects in studies in pregnant rabbits and the benserazide component has been found to be associated with skeletal malformations in the rat. If pregnancy occurs in a woman taking Madopar, the drug must be discontinued. Patients taking Madopar must not breast-feed their infants.

## **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 also section 4.4).

## 4.8 Undesirable effects

### *Gastro-intestinal:*

- Anorexia, nausea, vomiting, diarrhoea (less commonly than with levodopa) mainly occurring in the early stages of treatment may be controlled by taking with some food or liquid or increasing the dose slowly.
- Gastro-intestinal bleeding has been reported with levodopa therapy.
- Isolated cases of loss or alterations of taste.

### *Skin:*

- Rarely allergic reactions such as pruritus and rash.

### *Cardiovascular:*

- Occasional reports of cardiac arrhythmias and orthostatic hypotension (less frequently than with levodopa alone). Orthostatic disorders usually improve following dosage reduction.

### *Haematological:*

- Rare cases of haemolytic anaemia, transient leucopenia and thrombocytopenia.

### *Neuropsychiatric:*

- 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.
- Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.
- Patients treated with dopamine agonists and/or levodopa for treatment of Parkinson's disease, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.
- Involuntary movements (e.g. choreiform or athetotic, oral dyskinesias, "paddling" foot) are common, particularly on long-term administration. These are usually dose-dependent and may disappear or become tolerable after dose adjustment.

### *Laboratory abnormalities:*

- Transient rises in SGOT, SGPT and alkaline phosphatase values have been noted.
- Serum uric acid and blood urea nitrogen levels are occasionally increased.

### *Others:*

- Flushing and sweating have been reported with levodopa.
- Urine passed during treatment may be altered in colour; usually red-tinged, this will turn dark on standing. These changes are due to metabolites and are no cause for concern.

Tolerance to Madopar varies widely between patients and is often related to the rate of dosage increases.

## 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).

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 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).

In addition, for Madopar CR further absorption should be prevented using an appropriate method.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Madopar CR is a controlled release formulation of levodopa and the peripheral decarboxylase inhibitor benserazide, in the ratio of 4:1. Levodopa is the precursor of the neurotransmitter dopamine, the levels of which are reduced in Parkinsonism.

### 5.2 Pharmacokinetic properties

#### *Absorption*

Following oral administration of Madopar CR maximum plasma concentration, which are 20 - 30% of those achieved with standard Madopar, are reached approximately 3 hours after administration, and 5 hours after post-prandial administration. Bioavailability of Madopar CR is 50 – 70% of that of standard Madopar and is not affected by food.

#### *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 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-methyldopa.

Benserazide is hydroxylated to trihydroxybenzylhydrazine 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

None stated.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Capsule contents

Hypromellose (E464)  
Hydrogenated vegetable oil  
Calcium phosphate (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 the 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 Limited  
6 Falcon Way  
Shire Park  
Welwyn Garden City  
AL7 1TW  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER**

PA 50/43/7

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

Date of first authorisation: 05 October 1988

Date of last renewal: 01 April 2009

**10 DATE OF REVISION OF THE TEXT**

April 2009