IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0050/043/001
Case No: 2056944

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 100mg/25mg 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

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Madopar 100mg/25mg 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

Capsules, hard (Capsules)
Pale pink 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

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

The daily dosage should then be increased by one capsule 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 capsule 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 capsules of Madopar 100mg/25mg (two to four capsules of Madopar 200mg/50mg) daily in divided doses, most patients requiring no more than six capsules 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 capsules 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 capsules 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 capsules without, however, altering the total daily dose.

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

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

Madopar capsules are for oral administration. They should be taken with, or immediately after, meals.

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.

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.

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.

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

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

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

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.

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

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.

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 Section 4.4).

4.8 Undesirable effects

Gastrointestinal:

- Anorexia, nausea, vomiting, diarrhoea (less commonly than with levodopa) mainly occurring in the early stages of treatment. May be controlled by taking Madopar 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 wth 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-dependant 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. 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.

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 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 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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Microcrystalline cellulose (E460)
Povidone (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 HDPE cap with integral 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
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Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 50/43/1

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

April 2009