IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0002/072/003
Case No: 2040468

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

Bristol-Myers Squibb Pharmaceuticals Ltd

Swords, **Co. Dublin**, **Ireland**

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

Carace Tablets 20 mg.

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 **23/02/2008**.

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

Carace Tablets 20 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of lisinopril (as dihydrate).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.
Orange, half-scored, oval tablets, marked 'CARACE' and '20'.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension

All grades of essential hypertension and renovascular hypertension. "Carace" may be used alone or with other antihypertensive agents.

Heart Failure

In heart failure, "Carace" is indicated as adjunctive therapy with non-potassium-sparing diuretics and, where appropriate, digitalis.

Severe Heart Failure

Treatment with "Carace" should always be initiated in hospital under close medical supervision.

Mild to Moderate Heart Failure

Treatment with "Carace" should always be initiated under close medical supervision.

Acute Myocardial Infarction

"Carace" is indicated for the treatment of haemodynamically stable patients within 24 hours of acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blocker.

4.2 Posology and method of administration

The absorption of "Carace" is not affected by food. "Carace" should be administered in a single dose. As with all single daily dose medications, "Carace" should be taken at approximately the same time each day.

Hypertension

The need for dosage titration should be determined by measurement of the blood pressure just before the next dose.

Essential hypertension

In patients with essential hypertension the usual recommended starting dose is 10mg. The usual effective maintenance dosage is 20mg administered in a single daily dose. Dosage should be adjusted according to blood pressure response. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy. The maximum dose used in long-term, controlled clinical trials was 80 mg/day.

Renovascular Hypertension

Some patients with essential hypertension, especially those with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, may develop an exaggerated response to the first dose of "Carace". Therefore, a lower dose of 2.5 or 5 mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

Diuretic-treated patients

Symptomatic hypotension can occur following initiation of therapy with "Carace"; this is more likely when "Carace" is added to previous diuretic therapy. Caution is recommended, therefore, since these patients may be volume or salt depleted.

If possible, the diuretic should be discontinued, or the dose reduced, two to three days before beginning therapy with "Carace" (*see section 4.4., Special warnings and precautions for use*) and may be resumed later if required. In such diuretic-treated patients, therapy with "Carace" should be initiated with a 5 mg dose. The subsequent dosage of "Carace" should be adjusted according to blood pressure response.

"Carace" reduces the development of thiazide-induced hypokalaemia and hyperuricaemia.

Use in the elderly

Age alone does not appear to affect the efficacy or safety profile of "Carace". Thus, elderly patients should start treatment with "Carace" as directed above, except where there is renal impairment.

Congestive heart failure

"Carace" can be used as adjunctive therapy with non-potassium-sparing diuretics and/or digitalis. "Carace" should be introduced for the treatment of heart failure following stabilisation of the patient on diuretic therapy.

Therapy with "Carace" should be initiated under close medical supervision (in hospital for severe heart failure) with a recommended starting dose of 2.5 mg once daily. The dose of "Carace" should be gradually increased, depending upon tolerability to the recommended maintenance dose (5-20 mg) given as a single dose.

The dose titration of "Carace" may be performed over a two to four-week period or more rapidly if indicated by the presence of residual signs and symptoms of heart failure. Blood pressure and renal function should be monitored closely both before and during treatment with "Carace" because severe hypotension and more rarely consequent renal failure have been reported with angiotensin - converting enzyme (ACE) inhibitors. Serum potassium should also be monitored.

In order to decrease the possibility of symptomatic hypotension, patients previously on high-dose diuretics should have the diuretic dose reduced before introducing "Carace". The appearance of hypotension after the initial dose of "Carace" does not preclude subsequent careful dose titration with the drug, following effective treatment of the hypotension.

a) Initial Dose

Treatment should be initiated with a starting dose of 2.5 mg. If possible, the dose of diuretic should be reduced before beginning treatment.

b) Maintenance Dosage

The dosage should be gradually increased, depending on the patient's response to the usual maintenance dose (5-20 mg). This dose adjustment may be performed over a two-to-four week period, or more rapidly if clinically indicated.

Impaired renal function

"Carace" is excreted by the kidney, and should be used with caution in patients with renal insufficiency. The recommended starting dose is 2.5 mg and should be adjusted according to the response.

"Carace" is dialysable. Dialysis patients may be given the usual dose of "Carace" on dialysis days. On the days when patients are not on dialysis the dosage should be tailored to the blood pressure response.

Acute Myocardial Infarction

Treatment with "Carace" may be started within 24 hours of the onset of symptoms. The first dose of "Carace" is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter. Patients with a low systolic blood pressure (120 mmHg or less) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2.5 mg orally (*see section 4.4., Special warnings and precautions for use*). If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reduction to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour) "Carace" should be withdrawn.

Dosing for patients with acute myocardial infarction should continue for 6 weeks. For patients who develop symptoms of heart failure see Dosage and Administration, Congestive Heart Failure.

"Carace" is compatible with intravenous or transdermal glyceryl trinitrate.

Paediatric Use

"Carace" has not been studied for use in children.

4.3 Contraindications

1. "Carace" is contraindicated in patients who are hypersensitive to any component of this product.

2. "Carace" is contraindicated in patients with a history of angioneurotic oedema relating to previous treatment with angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

3. Use in patients with cor pulmonale or outflow tract obstruction.

4. Use in patients with aortic stenosis.

5. The use of "Carace" in pregnancy and in women breast feeding infants is contraindicated *(see section 4.6, Pregnancy and Lactation).*

4.4 Special warnings and precautions for use

General

Treatment of severe congestive heart failure with lisinopril should be introduced under hospital conditions in specialist units with adequate facilities for monitoring of clinical and laboratory response.

Where "Carace" is used as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Assessment of renal function

Evaluation of the patient should include assessment of renal function prior to initiation of therapy, and during treatment.

Impaired renal function

"Carace" should be used with caution in patients with renal insufficiency, as they may require reduced or less frequent doses (*see section 4.2., Posology and method of administration*). Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with ACE inhibitors and has been mainly in patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when "Carace" has been given concurrently with a diuretic. Dosage reduction of "Carace" and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 'Renovascular hypertension').

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. It is more likely to occur in patients who have been volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. In these patients, by discontinuing diuretic therapy or significantly reducing the diuretic dose for two to three days prior to initiating "Carace", the possibility of this occurrence is reduced. By initiating therapy with a small dose (5 mg "Carace") the duration of any hypotensive effect may be lessened.

Similar caution and close supervision may apply also to patients with ischaemic heart or cerebrovascular disease in whom severe hypotension could result in a myocardial infarct or cerebrovascular accident. *(See section 4.8, Undesirable Effects)*.

In hypertensive patients, the pharmacological action of "Carace" may prevent the normal body response to hypotension in patients presenting with symptoms of hypovolaemic shock. Such depression of blood pressure should be corrected by volume expansion.

Severe hypotension has been reported with ACE inhibitors, mainly in patients with severe heart failure. Many of these patients were on a high dose of loop diuretics, and some had hyponatraemia or functional renal impairment. If hypotension develops, the patient should be placed in a supine position. Volume repletion with oral fluids or intravenous normal saline may be required. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with "Carace" may be restarted with careful dose titration following restoration of effective blood volume and pressure.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with "Carace". Such patients should be kept under close medical supervision. If such hypotension becomes symptomatic, a reduction of dose or discontinuation of "Carace" may become necessary.

The appearance of hypotension after the initial dose of 'Carace' does not preclude subsequent careful dose titration with the drug after effective management of hypotension.

Hypotension in Acute Myocardial Infarction

Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mgHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then "Carace" should be withdrawn.

Renovascular Hypertension

"Carace" can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients treated with diuretics and/or those with renal insufficiency. It may not be possible to achieve a maximal response in blood pressure and maintain adequate renal perfusion.

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction defined as serum creatinine concentration exceeding 177 micromol/1 and/or proteinuria exceeding 500mg/24h.

If renal dysfunction develops during treatment with "Carace" (serum creatinine concentration exceeding 265 micromol/1 or a doubling from the pre-treatment value) then the physician should consider withdrawal of "Carace".

Hypersensitivity/Angioneurotic oedema: *(See section 4.3, Contraindications*) Angioneurotic oedema has been reported with angiotensin-converting enzyme inhibitors, including "Carace". This may occur at any time during treatment. In such cases, "Carace" should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx likely to cause airways obstruction, appropriate therapy (which may include subcutaneous epinephrine (adrenaline) (0.5 ml 1:1,000) and/or measures to ensure a patent airway) should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. *(See section 4.3, Contraindications).*

Other hypersensitivity reactions have been reported.

Anaphylactoid reactions hymenoptera desensitisation: Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom (e.g. Bee or Wasp venom) have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withdrawing ACE inhibitor therapy prior to each desensitisation.

Haemodialysis patients: Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Anaphylactoid reactions during LDL apheresis: Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia In patients undergoing major surgery or during anaesthesia with agents that produce hypotension “Carace” blocks angiotensin, II formulation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents e.g. β-adrenoceptor blockers, calcium antagonists, methyldopa and diuretics may supplement the hypotensive effects of lisinopril.

Plasma potassium usually remains within normal limits, although a few cases of hyperkalaemia have occurred. If “Carace” is given with a diuretic, the likelihood of diuretic-induced hypokalaemia may be lessened. “Carace” may elevate plasma potassium levels in patients with renal failure. Potassium supplements, potassium-sparing diuretics and potassium-containing salts substitutes are not recommended.

Indomethacin may reduce the antihypertensive efficacy of lisinopril.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of ACE inhibitors may result in a further deterioration of renal function. These effects are usually reversible.

“Carace” has been used with nitrates without significant clinical interaction.

As lisinopril may reduce the elimination of lithium, serum levels of lithium should be monitored if lithium salts are administered.

“Carace” reduces the development of thiazide-induced hypokalaemia and hyperuricaemia.

Epidemiological studies have suggested that concomitant administration of ACE-inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia; however, long-term controlled clinical trials with lisinopril have not confirmed these findings.

Alcohol may enhance the hypotensive effect of any antihypertensive.

Narcotic drugs/antipsychotics: Postural hypotension may occur with ACE-inhibitors.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids, or procainamide: Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia.

Antacids: induce decreased bioavailability of ACE inhibitors.

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored to confirm that the desired effect is being obtained.

Ciclosporins: increase the risk of hyperkalaemia with ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy

"Carace" has been shown to be foetotoxic in rabbits during middle and late pregnancy.

Effects of exposure of the foetus to ACE inhibitors during the first trimester of human pregnancy are unknown. Foetal exposure during the second and third trimesters of pregnancy has been associated with foetal and neonatal morbidity and mortality.

ACE inhibitors in human pregnancy have been associated with oligohydramnios. Hypotension and renal failure have occurred in the new-born.

Because of these findings "Carace" is contraindicated in pregnancy.

When pregnancy is detected, treatment with "Carace" should be discontinued as soon as possible.

Lactation

It is not known whether lisinopril is excreted in human milk; however, other ACE inhibitors do appear in human milk. "Carace" is contraindicated in women breast-feeding infants.

4.7 Effects on ability to drive and use machines

No data are known about the effect on the ability to drive and to operate machinery.

4.8 Undesirable effects

Hypotension has occurred in association with therapy with "Carace". This appears to occur in certain specific sub-groups *(see section 4.4., Special warnings and precautions for use).*

Hypersensitivity/angioneurotic oedema:

Angioneurotic oedema of face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (*see section 4.3. and 4.4.).* Intestinal angioedema has also been reported very rarely in patients treated with ACE inhibitors and should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Other adverse reactions
Dizziness, headache, diarrhoea, fatigue, cough, and nausea are the most frequent. Other less frequent side effects include: orthostatic effects (including hypotension), rash and asthenia.

Rare side effects include:

Cardiovascular: myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients *(see section 4.4.,Special warnings and precautions for use)*, palpitation, tachycardia**,** angina pectoris, rhythm disturbances.

Gastrointestinal: pancreatitis, abdominal pain, dry mouth, hepatitis (hepatocellular or cholestatic), jaundice, constipation, dyspepsia, vomiting.

Nervous system/psychiatric: mood alterations, mental confusion, paraesthesia**,** depression, insomnia, somnolence, vertigo.

Respiratory: bronchospasm**,** bronchitis, dyspnoea, nasal congestion, rhinitis, sinusitis.

Skin: urticaria, pruritus, diaphoresis, alopecia, erythema multiforme, pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Urogenital: uraemia, oliguria/anuria, renal dysfunction, acute renal failure, impotence.

Other: syncope, blurred vision, taste disturbances.

There have been reports of haemolytic anaemia in patients taking lisinopril, although no causal relationship has been established.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity, or other dermatological manifestations may occur.

Laboratory Test Findings

Increase in blood urea and creatinine, reversible on discontinuation of "Carace", are most likely in the presence of bilateral renal artery stenosis, especially in patients with renal insufficiency (*see section 4.4., Special warnings and precautions for use*). However, increase in blood urea and creatinine may occur without evidence of pre-existing renal impairment, especially in patients taking diuretics. In this event, undiagnosed renal artery stenosis should be suspected. Dosage reduction of "Carace" and/or discontinuation of the diuretic should be considered. Rare cases of neutropenia have been reported, although no causal relationship has been shown.

Increase in liver enzyme and serum bilirubin have occurred which are usually reversible on discontinuation of "Carace".

Bone marrow depression, manifest as anaemia and/or thrombocytopenia and/or leucopenia, has been reported.

Decreases in haemoglobin and haematocrit have been reported in a few patients, but were rarely of clinical importance unless another cause of anaemia was present.

Hyperkalaemia and hyponatraemia have occurred occasionally (see also 'Plasma potassium').

4.9 Overdose

The most likely manifestation of overdosage would be hypotension, which can be treated, if necessary, by intravenous infusion of normal saline solution, if available, angiotensin II may be beneficial. "Carace" can be removed by haemodialysis. *(see section 4.4., Special warnings and precautions for use -Haemodialysis Patients).*

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

"Carace" has been shown to inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased aldosterone secretion. ACE is identical to kininase, the enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of "Carace" remains to be elucidated. While the mechanism through which "Carace" lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, "Carace" has been shown to be antihypertensive even in patients with low-renin hypertension.

5.2 Pharmacokinetic properties

In most patients the onset of action was seen 1-2 hours following oral administration, with the maximum effect usually occurring by six hours. Declining serum concentrations exhibited a prolonged terminal phase which did not contribute to drug accumulation. "Carace" did not appear to be bound to plasma proteins other than ACE. Upon multiple dosing, "Carace" exhibited an effective half-life of accumulation of 12 hours. "Carace" does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery in clinical studies, the extent of absorption of "Carace" was approximately 25%. Absorption of "Carace" was not influenced by the presence of food in the gastrointestinal tract.

Single daily doses of "Carace" 5 mg were given for seven consecutive days to young and elderly healthy volunteers and to elderly patients with congestive heart failure. Maximum serum concentrations of "Carace" on Day 7 were higher in the elderly volunteers than in the young, and still higher in the elderly patients with congestive heart failure.

The disposition of "Carace" in patients with renal insufficiency was similar to that in patients with normal renal function until the glomerular filtration rate reached 30 ml/min or less, peak and trough levels of "Carace" then increased, and time to peak concentration was increased and to steady state sometimes prolonged.

5.3 Preclinical safety data

No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate
Magnesium stearate
Pregelatinised maize starch
Mannitol
Maize starch
Red iron oxide (E172)
Yellow 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.

6.5 Nature and contents of container

PVC/Aluminium blister packs of 28 tablets.

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

Bristol-Myers Squibb Pharmaceuticals Limited
Swords
County Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0002/072/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 May 1989

Date of last renewal: 23 February 2008

10 DATE OF REVISION OF THE TEXT

March 2009