Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carace 10 Plus Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg lisinopril as dihydrate and 12.5 mg hydrochlorothiazide.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Blue, hexagonal, biconvex tablet with the product code '145' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension where a further reduction in blood pressure is required following the use of 20 mg lisinopril. Management of hypertension in patients who have been stabilised on the individual components.

4.2 Posology and method of administration

Adults

Essential hypertension
The usual dosage is one tablet, taken once daily. If necessary, the dosage may be increased by a small increment of either constituent.

Dosage renal insufficiency
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30ml/min or below (i.e. moderate or severe renal insufficiency).

Carace 10 Plus is not to be used as initial therapy in any patient with renal insufficiency. In patients for whom therapy with Carace 10 Plus is intended, the state of renal function will have been established before introduction of lisinopril. Should there be pre-existing renal dysfunction, patients should be kept under regular surveillance for effects on blood urea and serum creatinine.

In patients with creatinine clearance of >30 and < 80 ml/min, Carace 10 Plus may be used, but only after titration of the individual components.

Prior Diuretic Therapy
Symptomatic hypotension may occur following the initial dose of Carace 10 Plus: this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. If possible, the diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Carace 10 Plus. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Use in the elderly

Lisinopril was equally effective in elderly (65 years or older) and non-elderly hypertensive patients.

In elderly hypertensive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Paediatric Use

Safety and effectiveness in children have not been established.

4.3 Contraindications

Use in patients with anuria, or aortic stenosis or hyperkalaemia.

Use in patients who are hypersensitive to any component of the product.

Use in patients with a history of angioneurotic oedema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

Use in patients who are hypersensitive to other sulphonamide-derived drugs.

Use in acute hypertension.

Use in congestive heart failure due to a lack of clinical data with the fixed combination. This fact has no bearing on the use in heart failure of the individual components which are effective treatment either alone or in combination when titrated appropriately.

Use 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

Hypotension and Electrolyte/Fluid Imbalance
As with all anti-hypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients but is more likely in the presence of fluid or electrolyte imbalance, e.g. volume depletion hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur from prior diuretic therapy, dietary salt restriction, dialysis, or during intercurrent diarrhoea or vomiting. Diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Carace 10 Plus. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Particular consideration should be given when therapy is administered to patients with ischaemic heart or cerebrovascular disease because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

Aortic stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Renal Function Impairment
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency). Carace 10 Plus should not be administered to patients with renal insufficiency (creatinine clearance < 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy with Carace 10 Plus, the combination should be discontinued. Reinstitution of therapy at reduced dosage may be possible, or either of the components may be used appropriately alone.

In some patients, with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen with angiotensin converting enzyme (ACE) inhibitors.

Patients who are being treated with this preparation require regular supervision with monitoring of fluid and electrolyte state to avoid inadequate potassium supplementation or excessive loss of fluid and to detect any development of renal dysfunction which might require discontinuation of Carace 10 Plus.

The preparation should be used with particular care in elderly patients or in patients with disorders rendering their electrolyte balance precarious.

Hepatic Disease
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of anti-diabetic agents, including insulin, may be required.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochorothiazide.

Hypersensitivity/angioneurotic oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients with angiotensin-converting enzyme inhibitors, including lisinopril. This may occur at any time during treatment. In such cases, Carace 10 Plus should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.

In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy (which may include subcutaneous epinephrime adrenaline solution 1:1,000 (0.3 ml to 0.5 ml) 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 also 4.3 'Contraindications').

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy to bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Anaphylactoid Reactions during 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 withholding 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 anti-hypertensive agent. Carace 10 Plus is not recommended in patients on haemodialysis for renal failure.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Serum potassium
The potassium-losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril.

The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of Carace 10 Plus and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Anti-diabetic drugs (oral agents and insulin)
Epidemiological studies have suggested that concomitant administration of ACE-inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemia 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.

Lithium
Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity: concomitant use is not recommended. Refer to the prescribing information for lithium preparations before use of such preparations.

Narcotic drugs/anti-psychotics
Postural hypotension may occur with ACE inhibitors.

Alcohol
Alcohol may enhance the hypotensive effect of any hypotensive.

Other agents
Indomethacin may diminish the antihypertensive effect of concomitantly administered Carace 10 Plus. In some patients with compromised renal function that 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.

Other anti-hypertensive agents
Additive effects may occur. The concomitant administration of this preparation with cardiac glycosides of hypotensive agents may necessitate adjustment of the dosage of those drugs.

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.

Ciclosporin
Increase the risk of hyperkalaemia with ACE inhibitors.

Non-depolarising muscle relaxants
Thiazides may increase the responsiveness to tubocurarine.

When administered concurrently, the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension may occur.

Anti-diabetic drugs (oral agents and insulin)
Dosage adjustment of the anti-diabetic drug may be required.

Colestyramine and colestipol resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind to the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Non-steroidal anti-inflammatory drugs
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of diuretics.

4.6 Pregnancy and lactation

Use in pregnancy. ACE inhibitors have been shown to be fetotoxic in rabbits during the 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 hum and pregnancy have been associated with oligohydramnios. Hypotension and renal failure have occurred in the newborn.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

Use in lactating women who are breast-feeding infants. It is not known whether lisinopril is excreted in human milk. Thiazides do appear in human milk. Therefore, if use of Carace 10 Plus is deemed essential, breast feeding must stop.

4.7 Effects on ability to drive and use machines

Usually Carace 10 Plus does not interfere with the ability to drive and to operate machinery. Patients should be instructed to first determine how they respond to Carace 10 Plus before performing hazardous tasks.

4.8 Undesirable effects

Side-effects
Carace 10 Plus is usually well tolerated. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy. The side effects that have been observed have been limited to those reported previously with lisinopril or hydrochlorothiazide.

The most common clinical side effect was dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy.

Other, less frequent, side effects were headache, dry cough, fatigue, and hypotension including orthostatic hypotension.

Still less common were diarrhoea, nausea, vomiting, dry mouth, rash, gout palpitations, chest discomfort, muscle cramps and weakness, parasthesiae, asthenia and impotence.

Hypersensitivity/Andioneurotic Oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (see 4.4 ‘Special Warnings and Special Precautions for Use’). 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.

A symptom complex has been reported which may include some or all of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Laboratory test findings
Laboratory side effects have rarely been of clinical importance. Occasional hyperglycaemia, hyperuricaemia and hyperkalaemia or hypokalaemia have been noted. Usually minor and transient increases in blood urea nitrogen and serum creatinine have been seen in patients without evidence of pre-existing renal impairment. If such increases persist, they are usually reversible upon discontinuation of Carace 10 Plus. Small decreases in haemoglobin and haematocrit have been reported frequently in hypertensive patients treated with Carace 10 Plus but were rarely of clinical importance unless another cause of anaemia co-existed. Rare cases of neutropenia have been reported, although no causal relationship has been established. Rarely, elevation of liver enzymes and/or serum bilirubin have occurred, but a casual relationship to Carace 10 Plus has not been established.

Other side effects reported with the individual components alone, and which may be potential side effects with Carace 10 Plus, are:

Lisinopril
Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see 'precautions'), tachycardia, abdominal pain, mood alterations, mental confusion, broncho-spasm, urticaria, pruritus, diaphoresis, alopecia, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, hepatitis – either hepatocellular or cholestatic jaundice, bone marrow depression manifest as anaemia and/or thrombocytopenia and/or leucopenia, hyponatraemia. Rare cases of neutropenia have been reported, although no causal relationship has been established. There have been reports of haemolytic anaemia in patients taking lisinopril, although no causal relationship has been established.

Hydrochlorothiazide
Anorexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialo-adenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotising angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, toxic epidermal necrolysis, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance including hyponatraemia, muscle spasm, restlessness, transient blurred vision, renal failure, renal dysfunction and interstital nephritis.

4.9 Overdose

No specific information is available on the treatment of overdosage with Carace 10 Plus. Treatment is symptomatic and supportive. Therapy with Carace 10 Plus should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Lisinopril
The most likely features of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline, if available angiotensin II may be beneficial.

Lisinopril may be removed from the general circulation by haemodialysis. (See 4.4 Precautions, Haemodialysis Patients).

Hydrochlorothiazode
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Carace 10 Plus is a fixed combination of angiotensin-converting enzyme inhibitor (lisinopril) and a diuretic (hydrochlorothiazide). Carace 10 Plus is highly effective in the treatment of hypertension. Hydrochlorothiazide stimulates the renin-angiotensin-aldosterone system and produced an additive anti-hypertensive effect with lisinopril which is sustained for at least 24 hours.

Hydrochlorothiazide is a diuretic and anti-hypertensive agent which increases plasma renin activity.

5.2 Pharmacokinetic properties

In clinical studies, peak serum concentrations of lisinopril occurred within about 6 to 8 hours following oral administration. Declining serum concentrations exhibited a prolonged terminal phase which did not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and was not proportional to dose. Lisinopril did not appear to be bound to plasma proteins.

Lisinopril does not undergo significant metabolism and is excreted unchanged predominantly in the urine. Based on urinary recovery in clinical studies, the extent of absorption of lisinopril was approximately 25%. Lisinopril absorption was not influenced by the presence of food in the gastrointestinal tract.

On multiple dosing, lisinopril exhibited an effective accumulation half-life of 1 hour.

Hydrochlorothiazide is not metabolised and is excreted through the kidney. Plasma elimination T½ is between 5.5-15 hours.

5.3 Preclinical safety data

Lisinopril and hydrochlorothiazide are well established in medical use. Preclinical data is broadly consistent with clinical experience. For reproduction toxicity, see section 4.6 ‘Pregnancy and Lactation’.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Calcium Hydrogen Phosphate Dihydrate
Indigo Carmine (E132)
Maize Starch
Pregelatinised Starch
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

30 months.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the blister in the outer carton.

6.5 Nature and contents of container

PVC/AL blister pack 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 Ltd
Swords
Co Dublin

8 MARKETING AUTHORISATION NUMBER

PA 0002/073/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd January 1995

Date of last renewal: 3rd January 2005

10 DATE OF REVISION OF THE TEXT

July 2006