IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1473/027/001
Case No: 2059739

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

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

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

Coversyl Arginine 5mg Film-coated Tablets

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 **31/07/2009**.

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

Coversyl Arginine 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains perindopril 3.395mg corresponding to perindopril arginine 5mg
Excipient : contains lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Product imported from UK:
Light-green, rod-shaped film-coated tablet engraved with  on one face and scored on both edges.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:

Treatment of hypertension.

Heart failure:

Treatment of symptomatic heart failure.

Stable coronary artery disease:

Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

4.2 Posology and method of administration

It is recommended that Coversyl Arginine 5 mg, film-coated tablet is taken once daily in the morning before a meal.

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension:

Coversyl Arginine 5 mg may be used in monotherapy or in combination with other classes of antihypertensive therapy.

The recommended starting dose is 5 mg given once daily in the morning.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2.5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

The dose may be increased to 10 mg once daily after one month of treatment.

Symptomatic hypotension may occur following initiation of therapy with Coversyl Arginine 5 mg; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Coversyl Arginine 5 mg (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Coversyl Arginine should be initiated with a 2.5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Coversyl Arginine should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2.5 mg which may be progressively increased to 5 mg after one month then to 10 mg if necessary depending on renal function (see table below).

Symptomatic heart failure:

It is recommended that Coversyl Arginine, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2.5 mg taken in the morning. This dose may be increased after 2 weeks to 5 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see section 4.4).

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Coversyl Arginine. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Coversyl Arginine 5 mg (see section 4.4).

Stable coronary artery disease:

COVERSYL ARGININE should be introduced at a dose of 5mg once daily for two weeks, then increased to 10mg once daily, depending on renal function and provided that the 5mg dose is well tolerated.
Elderly patients should receive 2.5mg once daily for one week, then 5mg once daily the next week, before increasing the dose up to 10mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:
Table 1: dosage adjustment in renal impairment

Creatinine clearance (ml/min)	Recommended dose
$Cl_{CR} \geq 60$	5 mg per day
$30 < Cl_{CR} < 60$	2.5 mg per day
$15 < Cl_{CR} < 30$	2.5 mg every other day
Haemodialysed patients *	
$Cl_{CR} < 15$	2.5 mg on the day of dialysis

* Dialysis clearance of perindoprilat is 70 ml/min.

For patients on haemodialysis, the dose should be taken after dialysis.

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2)

Paediatric use:

Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications

• Hypersensitivity to perindopril, to any of the excipients or to any other ACE inhibitor;

• History of angioedema associated with previous ACE inhibitor therapy;

• Hereditary or idiopathic angioedema*;*

• Second and third trimesters of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Stable coronary artery disease:

If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension:

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom 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 sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Coversyl Arginine 5 mg. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Coversyl Arginine 5 mg may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

As with other ACE inhibitors, Coversyl Arginine 5 mg should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Impairment of renal function:

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Coversyl Arginine 5 mg therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Coversyl Arginine 5 mg has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Coversyl Arginine 5 mg may be required.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Kidney transplantation:

There is no experience regarding the administration of Coversyl Arginine 5 mg in patients with a recent kidney transplantation.

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Coversyl Arginine 5 mg (see section 4.8). This may occur at any time during therapy. In such cases, Coversyl Arginine 5 mg should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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).

Anaphylactoid reactions during low-density lipoproteins (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.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Kidney transplantation:

There is no experience regarding the administration of Coversyl Arginine 5 mg in patients with a recent kidney transplantation.

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Coversyl Arginine 5 mg (see section 4.8). This may occur at any time during therapy. In such cases, Coversyl Arginine 5 mg should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

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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.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics:

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:

The administration of a non-steroidal anti-inflammatory drug may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

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. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

4.6 Pregnancy and lactation

Pregnancy:

Coversyl Arginine 5 mg, film-coated tablet should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human fetotoxicity as described below.

Perindopril is contraindicated during the second and third trimesters of pregnancy.

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, retardation of skull ossification) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to perindopril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Coversyl Arginine 5 mg, film-coated tablet is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Blood and the lymphatic system disorders:

Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4).

Psychiatric disorders:

Uncommon: mood or sleep disturbances.

Nervous system disorders:

Common: headache, dizziness, vertigo, paresthaesia.

Very rare: confusion.

Eye disorders:

Common: vision disturbance.

Ear and labyrinth disorders:

Common: tinnitus.

Vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Cardiac disorders:

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea.

Uncommon: bronchospasm.

Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders:

Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation.

Uncommon: dry mouth.

Very rare: pancreatitis.

Hepato-biliary disorders:

Very rare: hepatitis either cytolytic or cholestatic (see section 4.4).

Skin and subcutaneous tissue disorders:

Common: rash, pruritus.

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).

Very rare: erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps.

Renal and urinary disorders:

Uncommon: renal insufficiency.

Very rare: acute renal failure.

Reproductive system and breast disorders:

Uncommon: impotence.

General disorders:

Common: asthenia.

Uncommon: sweating.

Investigations:

Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

Clinical Trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain

ATC code: C09A A 04

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

Hypertension:

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media:lumen ratio of small arteries.

An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure:

Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Studies in patients with heart failure have demonstrated:

• decreased left and right ventricular filling pressures,
• reduced total peripheral vascular resistance,
• increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2.5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8mg perindopril tert-butylamine (equivalent to 10mg perindopril arginine) (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8mg perindopril tert-butylamine (equivalent to 10mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95% CI [9.4; 28.6] - $p<0.001$).

In patients with a history of myocardial infarction and/or revasularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95% CI [12.0; 31.6] - $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

5.3 Preclinical safety data

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

No mutagenicity has been observed in *in vitro* or *in vivo* studies.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maltodextrin
Hydrophobic colloidal silica
Sodium starch glycolate (type A)
Magnesium stearate

Film-coating:
Glycerol (E422a)
Hypromellose (E464)
Copper chlorophyll (E141 ii)
Macrogol
Magnesium stearate
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the county of origin.

6.4 Special precautions for storage

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

30 tablets in a white polypropylene tablet container equipped with a polyethylene flow reducer and a green opaque stopper containing a desiccant gel in an over labelled outer carton

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

Medicines no longer required should not be disposed of via the waster or the municipal sewage system. Return them to a pharmacy or ask your pharmacist how to dispose of them in accordance with the national regulations. These measured will help to protect the environment.

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals
4 Altona Road
Lisburn
BT27 5QB
Northern Ireland

8 Parallel Product Authorisation Number

PPA 1473/27/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st July 2009

10 DATE OF REVISION OF THE TEXT