IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA0465/067/003
Case No: 2054664

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Coversyl Plus 4mg/1.25mg 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 **20/10/2008** until **02/08/2012**.

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

Coversyl Plus 4mg/1.25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:
Perindopril tert-butylamine 4.00 mg, equivalent to 3.338 mg perindopril
Indapamide 1.25 mg

Excipients: Lactose Monohydrate
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Product imported from the Netherlands:
White, rod-shaped tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension, COVERSYL PLUS 4mg/1.25mg Tablets are indicated in patients whose blood pressure is not adequately controlled on perindopril alone

4.2 Posology and method of administration

Oral route

One COVERSYL PLUS 4mg/1.25mg tablet per day as a single dose, preferably to be taken in the morning, and before a meal.

When possible individual dose titration with the components can be recommended. When clinically appropriate, direct change from monotherapy to COVERSYL PLUS 4mg/1.25mg Tablets may be considered.

Patients with renal insufficiency (see Special warnings and special precautions for use).

In severe renal insufficiency (creatinine clearance below 30 ml/min), treatment is contra-indicated.

In patients with creatinine clearance greater than or equal to 30 ml/min and less than 60 ml/min, it is recommended to start treatment with the adequate dosage of the free combination. It is not necessary to change the dose when creatinine clearance is greater than 60 ml/min. Usual medical follow-up will include frequent monitoring of creatinine and potassium.

Children
COVERSYL PLUS 4mg/1.25mg Tablets should not be used in children as the efficacy and tolerability of perindopril in children, alone or in combination, have not been established.

4.3 Contraindications

LINKED TO PERINDOPRIL:

• Hypersensitivity to perindopril or any other ACE inhibitor

• History of angioneurotic oedema (Quincke's oedema) associated with previous ACE inhibitor therapy

• Hereditary/idiopathic angioneurotic oedema

• Pregnancy

• Lactation

• The drug is usually not recommended in case of: - Combinations with potassium-sparing diuretics, potassium salts, lithium (see Interactions with other medicaments)

- Bilateral renal artery stenosis or single functioning kidney.

- Raised plasma levels of potassium.

LINKED TO INDAPAMIDE:

• Hypersensitivity to sulphonamides

• Severe renal failure (creatinine clearance below 30 ml/min)

• Hepatic encephalopathy

• Severe impairment of liver function

• Hypokalaemia

• As a general rule, this medicine is inadvisable in combination with non-antiarrhythmic agents causing torsades de pointes (see Interactions with other medicaments).

LINKED TO COVERSYL PLUS 4MG/1.25MG TABLETS :

• Hypersensitivity to any of the excipients

Due to the lack of sufficient therapeutic experience, COVERSYL PLUS 4mg/1.25mg Tablets should not be used in:

• dialysis patients

• patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsoption should not take this medicine.

LINKED TO PERINDOPRIL:

RISK OF NEUTROPENIA/AGRANULOCYTOSIS IN IMMUNO-SUPPRESSED PATIENTS:

The risk of neutropenia appears to be dose and typerelated and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Strict compliance with the predetermined dose seems to be the best way to prevent the onset of these events. However, if an angiotensin converting enzyme inhibitor is to be administered to this type of patient, the risk/benefit ratio should be evaluated carefully.

ANGIONEUROTIC OEDEMA (QUINCKE'S OEDEMA):

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients receiving treatment with angiotensin converting enzyme inhibitors, including perindopril. In such cases, treatment with perindopril should be stopped immediately and the patient should be monitored until the oedema has disappeared.

When the oedema only affects the face and the lips, the effect generally recedes without treatment, even though antihistamines may be used to relieve symptoms.

Angioneurotic oedema combined with laryngeal oedema may be fatal. Involvement of tongue, glottis or larynx may lead to an obstruction of the airways.

A subcutaneous injection of adrenaline at 1:1000 (0.3 ml to 0.5 ml) should be administered quickly and other appropriate measures taken.

The prescription of an angiotensin converting enzyme inhibitor should not subsequently be considered in these patients (see Contra-indications).

Patients with a previous history of Quincke's oedema which was not linked to taking an angiotensin converting enzyme inhibitor have an increased risk of Quincke's oedema with an angiotensin converting enzyme inhibitor.

ANAPHYLACTIC REACTIONS DURING DESENSITISATION:

There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE-inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE-inhibitors should be used with caution in allergic patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However these reactions could be prevented by temporary withdrawal of ACE-inhibitor for at least 24 hours before treatment in patients who require both ACE-inhibitors and desensitisation.

ANAPHYLACTIC REACTIONS DURING MEMBRANE EXPOSURE :

There have been reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE-inhibitors during dialysis with high-flux membranes or low-density lipoprotein apheresis with dextran sulphate adsorption. ACE-inhibitors should be avoided in patients undergoing dialysis with high-flux membranes or LDL apheresis with dextran sulphate adsorption. However these reactions could be prevented by temporary withdrawal of ACE-inhibitor for at least 24 hours before treatment in patients who require both ACE-inhibitors and LDL apheresis.

LINKED TO INDAPAMIDE:

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic should be stopped immediately if this occurs.

Special precautions for use

LINKED TO COVERSYL PLUS 4MG/1.25MG TABLETS:

RENAL INSUFFICIENCY:
In cases of severe renal insufficiency (creatinine clearance < 30 ml/min), treatment is contra-indicated.

In certain hypertensive patients without pre-existing apparent renal lesion and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only.

In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

HYPOTENSION AND WATER AND ELECTROLYTE DEPLETION:

There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma electrolytes should be carried out in such patients.

Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contra-indication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

POTASSIUM LEVELS:
The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent containing a diuretic, regular monitoring of plasma potassium levels should be carried out.

LINKED TO PERINDOPRIL:

COUGH:
A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

CHILDREN:
The efficacy and tolerability of perindopril in children, alone or in combination, have not been established.

RISK OF ARTERIAL HYPOTENSION AND/OR RENAL INSUFFICIENCY (IN CASES OF CARDIAC INSUFFICIENCY, WATER AND ELECTROLYTE DEPLETION, ETC…):

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-free diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.

In such cases, the treatment should then be initiated at a lower dose and increased progressively.

ELDERLY:
Renal function and potassium levels should be tested before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.

PATIENTS WITH KNOWN ATHEROSCLEROSIS :
The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.

RENOVASCULAR HYPERTENSION:
The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.

Treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

OTHER POPULATIONS AT RISK:
In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

ANAEMIA:
Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors.

This reduction in haemoglobin is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

SURGERY:
Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential. It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible two days before surgery.

AORTIC STENOSIS / HYPERTROPHIC CARDIOMYOPATHY:

ACE inhibitors should be used with caution in patient with an obstruction in the outflow tract of the left ventricle.

LINKED TO INDAPAMIDE:

WATER AND ELECTROLYTE BALANCE:

Sodium levels:
These should be tested before treatment is started, then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see Undesirable effects and Overdose).

Potassium levels:
Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The risk of onset of lowered potassium levels (< 3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders.

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required.

Calcium levels:
Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

BLOOD GLUCOSE:

Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

URIC ACID:
Tendency to gout attacks may be increased in hyperuricaemic patients.

RENAL FUNCTION AND DIURETICS:
Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockroft formula: clcr = (140 - age) x body weight / 0.814 x plasma creatinine level with:

age expressed in years

body weight in kg

Plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal insufficiency.

ATHLETES:
Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

LINKED TO COVERSYL plus 4mg/1.25mg tablets:

Combinations which are NOT RECOMMENDED:

Lithium

An increase in lithium levels may produce signs of overdose, as occurs with a sodiumfree diet (reduction in renal excretion of lithium). If the combination of an angiotensin converting enzyme inhibitor and a diuretic is unavoidable, strict monitoring of lithium levels and adjustment of the dose are necessary.

Combinations which require special care:

Antidiabetic agents (insulin, hypoglycaemic sulphonamides)

Reported with captopril and enalapril

The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Baclofen

Potentiation of antihypertensive effect

Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

N.S.A.I.D (systemic route), high-dose salicylates

Acute renal insufficiency in dehydrated patients (reduction in glomerular filtration). The patient should be well hydrated; renal function should be monitored at the start of treatment.

Combinations which require some care:

Imipramine-like antidepressants (tricyclics), neuroleptics

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Corticosteroids, tetracosactide

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

LINKED TO PERINDOPRIL :

Combinations which are NOT RECOMMENDED:

Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination...), potassium (salts)

Increased levels of potassium (potentially lethal), particularly in cases of renal insufficiency (addition of potassium-sparing effects). Potassium-raising agents should not be combined with angiotensin converting enzyme inhibitors, except when potassium levels are low.

Anaesthetic drugs

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Antihypertensive agents

Increase of the hypotensive effect of ACE inhibitors.

LINKED TO INDAPAMIDE :

Combinations which are NOT RECOMMENDED:

Non antiarrhythmic drugs which prolong the QT interval or cause torsades de pointes (astemizole, bepridil, erythromycin IV, halofantrine, pentamidine, sultopride, terfenadine, vincamine)

Torsades de pointes (low potassium levels is a risk, as are bradycardia and pre-existing long QT interval). Substances which do not have the unwanted effect of causing torsades de pointes should be used in cases of low potassium levels.

Combinations which require special care:

N.S.A.I.D (systemic route), high-dose salicylates

Possible reduction in the antihypertensive effect of indapamide.

Acute renal insufficiency in dehydrated patients (reduction in glomerular filtration).

Hydrate the patient; monitor renal function at the start of treatment.

Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives

Increased risk of low potassium levels (additive effect).

Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non-stimulant laxatives should be used.

Cardiac glycosides

Low potassium levels favour the toxic effects of cardiac glycosides.

Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

Combinations which require some care:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)

The rational combination, which is useful for some patients, does not exclude the onset of low potassium levels or, particularly in patients with renal insufficiency or diabetes, raised potassium levels. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

Antiarrhythmic drugs which produce torsades de pointes: Class 1A antiarrhythmic agents (quinidine, hydroquinidine, disopyramide), amiodarone, bretylium, sotalol

Torsades de pointes (low potassium levels is a risk factor, as are bradycardia and a pre-existing long QT interval).

Prevention of low potassium levels and correction if necessary: monitoring of the QT interval. Antiarrythmics should not be administered in cases of torsades de pointes (management by pacemaker).

Metformin

Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics.

Do not use metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (110 micromol/l) in women.

Iodinated contrast media

In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used.

Rehydration should be carried out before the iodinated compound is administered.

Imipramine-like antidepressants (tricyclics), neuroleptics

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Calcium (salts)

Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

Cyclosporin

Risk of increased creatinine levels with no change in circulating levels of cyclosporin, even when there is no salt and water depletion.

Corticosteroids, tetracosactide (systemic route)

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

4.6 Pregnancy and lactation

As this combination includes an ACE inhibitor, COVERSYL® PLUS 4mg/1.25mg Tablets are contra-indicated during pregnancy and lactation.

LINKED TO PERINDOPRIL:

Pregnancy:
Appropriate and wellcontrolled studies have not been done in humans. ACE inhibitors cross the placenta and can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Foetal exposure to ACE inhibitors during the second and third trimesters has been associated with neonatal hypotension, renal failure, face or skull deformities and/or death. Maternal oligohydramnios has also been reported reflecting decreasing renal function in the foetus. Limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. Oliguria should be treated with support of blood pressure and renal perfusion.

Intrauterine growth retardation, prematurity, patent ductus arteriosus and foetal death have also been reported but it is not clear whether they are related to the ACE inhibition or the underlying maternal disease.

It is not known whether exposure limited to the first trimester can adversely affect foetal outcome. Women who become pregnant while receiving an ACE inhibitor should be informed of the potential hazard to the foetus.

Lactation:
ACE inhibitors may be excreted in breast milk and their effect on the nursing infant has not been determined. It is recommended that lactating mothers should not breast feed while taking ACE inhibitors.

LINKED TO INDAPAMIDE :

Pregnancy:
As a general rule, the administration of diuretics should be avoided in pregnant women and should never be given as treatment for physiological oedema (and therefore do not require treatment) of pregnancy. Diuretics may lead to foeto-placental ischaemia, with a risk of impaired foetal growth.

Nonetheless diuretics remain an essential part of the treatment of oedema from cardiac, hepatic and renal origin arising in pregnant women.

Lactation:
Indapamide is excreted in small quantities in breast milk. Nonetheless, it should not be used in breast-feeding period due to:

• the decrease and even suppression of the milk secretion,

• its undesirable effects in particular biological (potassium levels),

• its belonging to the sulphonamide group with the risks of allergy and nuclear icterus.

4.7 Effects on ability to drive and use machines

LINKED TO PERINDOPRIL, INDAPAMIDE AND COVERSYL PLUS 4MG/1.25MG TABLETS:
Neither the two active substances nor COVERSYL® PLUS 4mg/1.25mg Tablets affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication. As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Four percent of the patients on treatment with COVERSYL® PLUS 4mg/1.25mg Tablets experience hypokalaemia (potassium level < 3.4 mmol/l).

GASTRO-INTESTINAL TRACT

• Common (>1/100, <1/10): constipation, dry mouth, nausea, epigastric pain, anorexia, abdominal pains, taste disturbance

• Very rare (<1/10,000): pancreatitis

• In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see Contra-indications and Special warnings)

RESPIRATORY SYSTEM

• Common (>1/100, <1/10): A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the presence of this symptom.

CARDIO-VASCULAR SYSTEM

• Uncommon (>1/1,000, <1/100): Hypotension whether orthostatic or not (see Special precautions for use).

SKIN APPENDAGES

• Uncommon (>1/1,000, <1/100): - Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions

- Maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus

- Skin rash

• Very rare (<1/10,000): Angioneurotic oedema (Quincke's oedema) (see Special warnings)

NERVOUS SYSTEM

• Uncommon (>1/1,000, <1/100): Headache, asthenia, feelings of dizziness, mood disturbances and/or sleep disturbances.

MUSCULAR SYSTEM

• Uncommon (>1/1,000, <1/100): Cramps, paresthesia.

HAEMIC SYSTEM

• Very rare (<1/10,000): - Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.

- Anaemia (see Special precautions for use) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

LABORATORY PARAMETERS

• Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see Special precautions for use).

• Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.

• Increase in uric acid levels and in blood glucose levels during treatment

• Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.

• Increased levels of potassium, usually transitory.

• Rare (>1/10,000, <1/1,000): raised plasma calcium levels.

4.9 Overdose

The most likely adverse event in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.

Perindoprilat, the active form of perindopril, can be dialysed (see Pharmacokinetic properties).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: perindopril and diuretics

ATC code: C09BA04

COVERSYL® PLUS 4mg/1.25mg Tablets are a combination of perindopril tert-butylamine salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

PHARMACOLOGICAL MECHANISM OF ACTION

LINKED TO COVERSYL PLUS 4MG/1.25MG TABLETS:

COVERSYL PLUS 4mg/1.25mg Tablets produce an additive synergy of the anti-hypertensive effects of the two components.

LINKED TO PERINDOPRIL:
Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

This results in:

• a reduction in aldosterone secretion,

• an increase in plasma renin activity, since aldosterone no longer exercises negative feedback,

• a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.

The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations.

Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive. Perindopril reduces the work of the heart:

• by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in pre-load,

• by reduction of the total peripheral resistance: reduction in afterload.

Studies carried out on patients with cardiac insufficiency have shown:

• a reduction in left and right ventricular filling pressures,

• a reduction in total peripheral vascular resistance,

• an increase in cardiac output and an improvement in the cardiac index,

• an increase in regional blood flow in muscle.

Exercise test results also showed improvement.

LINKED TO INDAPAMIDE:
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

CHARACTERISTICS OF ANTIHYPERTENSIVE ACTION

LINKED TO COVERSYL plus 4mg/1.25mg tablets:
In hypertensive patients regardless of age, Coversyl® Plus 4mg/1.25mg Tablets exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

LINKED TO PERINDOPRIL:
Perindopril is active in all grades of hypertension: mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position.

The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and is maintained over 24 hours.

There is a high degree of residual blocking of angiotensin converting enzyme at 24 hours, approximately 80%.

In patients who respond, normalised blood pressure is reached after one month and is maintained without tachyphylaxis.

Withdrawal of treatment has no rebound effect on hypertension.

Perindopril has vasodilatory properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.

If necessary, the addition of a thiazide diuretic leads to an additive synergy.

The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

LINKED to indapamide:

Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal.

Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.

Indapamide reduces left ventricular hypertrophy.

When a dose of thiazide diuretic and thiazide-related diuretics is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.

Furthermore, it has been shown that in the short-term, mid-term and long-term in hypertensive patients, indapamide:

• has no effect on lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol,

• has no effect on carbohydrate metabolism, even in diabetic hypertensive patients.

5.2 Pharmacokinetic properties

LINKED TO COVERSYL PLUS 4MG/1.25MG TABLETS:
The co-administration of perindopril and indapamide does not change their pharmacokinetic properties by comparison to separate administration.

LINKED TO PERINDOPRIL :
Perindopril is rapidly absorbed by the oral route. The quantity absorbed is 65 to 70 % of the dose administered. It is hydrolysed into perindoprilat which is a specific angiotensin converting enzyme inhibitor. The quantity of perindoprilat formed is altered by food intake. The peak plasma concentration of perindoprilat is reached after 3 to 4 hours. Plasma protein binding is less than 30 % but is concentration-dependent.

After repeated administration of perindopril as a single daily dose, steadystate is reached after an average of 4 days. The effective elimination halflife of perindoprilat is approximately 24 hours.

Plasma concentrations of perindoprilat are significantly higher in patients with creatinine clearance below 60 ml/min, whether they are patients with renal insufficiency or elderly. Elimination is also slowed down in patients with cardiac insufficiency.

The clearance of perindopril by dialysis is 70 ml/min.

In cirrhotic patients, the kinetics of perindopril is altered: hepatic clearance of the parent substance is reduced by half. However, the quantity of perindoprilat formed is not reduced and dose adjustment is therefore not necessary.

Angiotensin converting enzyme inhibitors cross the placenta.

LINKED TO INDAPAMIDE:
Indapamide is rapidly and completely absorbed from the digestive tract.

The peak plasma level is reached in humans approximately one hour after oral administration of the product. Plasma protein binding is 79 %.

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

The pharmacokinetics are unchanged in patients with renal insufficiency.

5.3 Preclinical safety data

COVERSYL PLUS 4mg/1.25mg Tablets have slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril).

Nonetheless, these adverse effects are shown at dose levels corresponding to a very marked safety margin by comparison to the therapeutic doses used.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal hydrophobic silica
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

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

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of 30 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 Parallel Product Authorisation Holder

PCO Manufacturing Ltd
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 Parallel Product Authorisation Number

PPA 465/67/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd August 2007

10 DATE OF REVISION OF THE TEXT

October 2008