VECTORYL® 4 mg

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

Vectoryl® 4 mg, tablet.

COMPOSITION:

Each **Vectoryl® 4 mg** tablet contains 4 mg perindopril tert-butylamine salt.

The other ingredients are: Hydrophobic colloidal silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Contains sugar (lactose) 62,78 mg.

CATEGORY AND CLASS:

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

A reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours.

In terms of trough versus peak blood pressure effect, the trough effect ranges between 75 – 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.

Reduction in blood pressure in patients treated with perindopril was accompanied by a reduction in peripheral resistance with no significant changes in heart rate or glomerular filtration rate. An increase in the compliance of large arteries was also observed, suggesting a direct effect on arterial smooth muscle. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

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,

Patients with stable coronary artery disease:

The effects of perindopril were compared to placebo in patients with stable coronary artery disease with no clinical signs of heart failure (see Summary of clinical studies).

Pharmacokinetic properties:

Following oral administration the absorption of perindopril is rapid and the peak concentration complete within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

The bioavailability of perindoprilat, the active metabolite, is 27 %. Apart from active perindoprilat, perindopril gives rise to 5 metabolites, all of which are inactive.

The peak concentration of perindoprilat, the active metabolite, is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours.

The ingestion of food decreases conversion to perindoprilat, and hence bioavailability. Therefore, perindopril should be administered orally as a single daily dose in the morning before breakfast.

The volume of distribution is approximately 0,2 l/kg for unbound perindoprilat. Protein binding is slight (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 slower in the elderly, as well as in patients with heart or renal failure. In such patients dosage adjustment should be made in relation to the degree of reduction in creatinine clearance.

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

Perindopril kinetics is 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.

Summary of clinical studies:

The **EUROPA** study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. 12 218 patients aged 18 and over were randomised: 6 110 patients to perindopril 8 mg and 6 108 patients to placebo.

The main evaluation criteria were the composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation.

The trial population had evidence of coronary artery disease documented by previous myocardial infarction at least 3 months before screening, coronary revascularisation at least 6 months before screening, angiographic evidence of stenosis (at least 70 % narrowing of one or more major coronary arteries), or positive stress test in men with a history of chest pain.

Study medication was added to conventional therapy, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Most of the patients received platelet inhibitors, lipid lowering agents and beta-blockers during the study. At the end of the study, the proportions of patients on these concomitant medications were 91 %, 69 % and 63 % respectively.

After a mean follow-up of 4,2 years, the treatment with perindopril 8 mg once daily resulted in a significant relative risk reduction of 20 % (95 % CI [9,4; 28,6]) in the primary combined endpoint: 488 (8,0 %) patients reported events in the perindopril group compared to 603 (9,9 %) patients in the placebo group (p = 0,0003).

The benefit was particularly marked with regard to the non-fatal myocardial infarction component of the composite endpoint.

The risk reduction was consistent irrespective of: gender, history of myocardial infarction, whether patients were hypertensive or not and diabetic or not.

INDICATIONS:

Vectoryl® 4 mg is indicated in:

- Mild to moderate hypertension.
- Congestive heart failure not adequately controlled by conventional therapy with diuretics and digitalis in whom vasodilatation is indicated.
- Reduction of risk of cardiovascular events in patients with stable coronary artery disease and without heart failure.

CONTRAINDICATIONS:

- Hypersensitivity to any of the ingredients of **Vectoryl®.**
- A history of angioedema associated with previous ACE-inhibitor therapy or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines. (see WARNINGS AND SPECIAL PRECAUTIONS).
- Hereditary or idiopathic angioedema.

- Hypertrophic obstructive cardiomyopathy (HOCM) (see WARNINGS AND SPECIAL PRECAUTIONS).
- Severe renal function impairment (creatinine clearance below 30 ml/min).
- Bilateral renal artery stenosis.
- Significant renal artery stenosis or stenosis of the artery to a single functioning kidney.
- Aortic stenosis (see WARNINGS AND SPECIAL PRECAUTIONS).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see INTERACTIONS).
- Porphyria.
- Lithium therapy: Concomitant use with **Vectoryl®** may lead to toxic blood concentration of lithium (see INTERACTIONS).
- Pregnancy and lactation (see WARNINGS AND SPECIAL PRECAUTIONS and HUMAN REPRODUCTION).
- Concomitant use of **Vectoryl®** with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m^2) (see INTERACTIONS).
- Concomitant use with sacubitril/valsartan (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS),
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see INTERACTIONS),
- Concomitant use with fluoroquinolones in patients with moderate to severe renal failure, such as elderly patients.

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving **Vectoryl®**, the treatment must be stopped promptly and switched to a different medicine (see CONTRAINDICATIONS and HUMAN REPRODUCTION). Should a woman contemplate pregnancy, the doctor should consider alternative medication.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **Vectoryl®** and aliskiren is therefore contraindicated (see CONTRAINDICATIONS).

Vectoryl® should not be used concomitantly with aliskiren. (see CONTRAINDICATIONS).

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 rarely seen 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 INTERACTIONS and SIDE EFFECTS).

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 with an increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see SIDE EFFECTS). 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 normal saline. A transient hypotensive response is not a contra-indication 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 **Vectoryl®.** If hypotension becomes symptomatic, a reduction of the dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

Vectoryl® 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.

Impaired renal function:

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial **Vectoryl®** dosage should be adjusted according to the patient's creatinine clearance (see DOSAGE AND DIRECTIONS FOR USE) and then as a function of the patient's response to treatment (see Renal Insufficiency). Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see SIDE EFFECTS).

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 has been reported in this situation.

In patients with bilateral renal artery stenosis, or stenosis of the artery to a solitary kidney, and who have been treated with ACE-inhibitors, increases in blood urea and serum creatinine may occur. This is usually reversible upon discontinuation of therapy.

It 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 **Vectoryl®** therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, especially when **Vectoryl®** was 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 **Vectoryl®** may be required.

Haemodialysis patients:

Anaphylactic 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 **Vectoryl®** in patients with a recent kidney transplant.

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patients with with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitors (see CONTRAINDICATIONS). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Hypersensitivity/Angioedema:

Angioedema of the face, lips, mucous membranes, tongue, glottis and/or larynx, and extremities has been reported, in patients treated with ACE-inhibitors**.** This may occur at any time during therapy. In such cases, **Vectoryl®** should immediately be discontinued and appropriate monitoring should be initiated and continued until the symptoms have disappeared completely. 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, and is likely to cause airway obstruction, emergency therapy should immediately be administered. This may include the administration of epinephrine (adrenaline) and/or the maintenance of the patient's airway. The patient should be under close medical supervision until the symptoms have disappeared.

ACE-inhibitors cause a higher rate of angioedema in black patients than in other ethnic groups.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor (see CONTRAINDICATIONS).

Intestinal angioedema has been reported in patients treated with ACE-inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE-inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE-inhibitors presenting with abdominal pain.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see CONTRAINDICATIONS). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see CONTRAINDICATIONS and INTERACTIONS).

Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE-inhibitors may also increase the risk of angioedema (see INTERACTIONS). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):
Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see INTERACTIONS).

Anaphylactic reactions during low-density lipoproteins (LDL) apheresis:

Patients receiving ACE-inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have rarely experienced life-threatening anaphylactic reactions. These reactions were avoided by temporarily withholding ACE-inhibitors therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactic reactions. These reactions were avoided when the ACE-inhibitors were temporarily withheld, but they reappeared upon re-challenge.

Hepatic failure:

ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice and suddenly progresses to 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 **Vectoryl®** and receive appropriate medical follow-up (see SIDE EFFECTS).

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 rarely occurs. **Vectoryl®** should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to

intensive antibiotic therapy. If **Vectoryl®** is used in such patients, periodic monitoring of the white blood cell count is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Race:

ACE-inhibitors cause a higher rate of angioedema in black patients than in other ethnic groups. **Vectoryl®** may be less effective in lowering blood pressure in black people than in other ethnic groups, possibly because of a higher prevalence of low-renin levels in the black hypertensive population.

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-inhibitors induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, **Vectoryl®** may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with **Vectoryl®**. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing

salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal dysrhythmias. If concomitant use of the above-mentioned agents is deemed necessary, regular monitoring of serum potassium is recommended (see INTERACTIONS).

Diabetic patients:

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with ACE-inhibitors (see INTERACTIONS).

Lithium:

The combination of lithium and **Vectoryl®** is generally not recommended (see INTERACTIONS).

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

The combination of **Vectoryl®** and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see INTERACTIONS).

Primary aldosteronism:

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive medication acting through inhibition of the renin-angiotensin system. Therefore, the use of **Vectoryl®** is not recommended.

Concomitant use of fluoroquinolones*:*

Concomitant use of fluoroquinolones and **Vectoryl®** may precipitate acute kidney injury (AKI) in patients, especially those with moderate to severe renal failure and elderly patients (see CONTRAINDICATIONS). Renal function should be assessed before initiating treatment and monitored during treatment, with concomitant use of fluoroquinolones and **Coversyl®** (see CONTRAINDICATIONS and INTERACTIONS).

Excipients:

Vectoryl® contains lactose**. Vectoryl®** should not be administered to patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia the Lapp lactase deficiency or glucose-galactose malabsorption.

Effect on ability to drive and use machines:

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

INTERACTIONS:

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren:

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Medicines inducing hyperkalaemia:

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE-inhibitors, angiotensin-II

receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim. The combination of these medicines increases the risk of hyperkalaemia.

Concomitant use contraindicated (see CONTRAINDICATIONS):

Aliskiren:

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal treatments:

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see CONTRAINDICATIONS). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Sacubitril/Valsartan:

The concomitant use of perindopril with sacubitril/valsartan is contra-indicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see WARNINGS AND SPECIAL PRECAUTIONS and CONTRAINDICATIONS).

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:

Concomitant use of fluoroquinolones and **Vectoryl®** may precipitate acute kidney injury (see CONTRAINDICATIONS). and WARNINGS AND SPECIAL PRECAUTIONS).

It has been reported that AKI occurred soon after ciprofloxacin was prescribed in patients taking enalapril. The interaction between ACE-inhibitors and fluoroquinolones to precipitate AKI is a class effect for all ACE-inhibitors and not just enalapril and also a class effect of all fluoroquinolones, not just with ciprofloxacin.

Concomitant use not recommended (see WARNINGS AND SPECIAL PRECAUTIONS):

Aliskiren:

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker:

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.

Estramustine:

Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Co-trimoxazole (trimethoprim/sulfamethoxazole):

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see WARNINGS AND SPECIAL PRECAUTIONS).

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 ACE-inhibitors**.** The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, and by increasing volume or salt intake prior to initiating therapy with low and increasing doses of perindopril.

Potassium sparing diuretics, (e.g. triamterene, amiloride,...), potassium salts:

Hyperkalaemia may occur in some patients treated with **Vectoryl®**. The combination of **Vectoryl®** with the above-mentioned medicines is not recommended (see WARNINGS AND SPECIAL PRECAUTIONS) . If concomitant use is indicated because of confirmed hypokalaemia, they should be used with caution and serum potassium should frequently be monitored. For use of spironolactone in heart failure, (see below Potassium-sparing diuretics (eplerenone, spironolactone).

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. Combination of **Vectoryl®** with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see WARNINGS AND SPECIAL PRECAUTIONS).

Concomitant use which requires special care:

Antidiabetic agents (insulins, oral hypoglycaemic 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 the risk of hypoglycaemia. This phenomenon appeared to be more likely during the first weeks of combined treatment and in patients with renal impairment.

Baclofen:

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing 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.

In arterial hypertension:

When prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE-inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE-inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure:

Vectoryl® should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE-inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)

With eplerenone or spironolactone at doses between 12,5 mg to 50 mg by day and with low doses of ACE-inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and previously treated with ACE-inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

Close monitoring of the potassium and creatinine is recommended in the first month of the treatment, once a week at the beginning and then, monthly thereafter.

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

The administration of non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) 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, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Racecadotril:

ACE-inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a medicine used against acute diarrhoea).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see WARNINGS AND SPECIAL PRECAUTIONS).

Concomitant use which requires some care:

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of **Vectoryl®**. Concomitant use with nitro-glycerin 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 the risk of hypoglycaemia. This phenomenon appeared to be more likely during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers and nitrates:

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

Gliptines (linagliptine, saxagliptine, sitagliptine, vildagliptine) :

Increased risk of angioedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptine, in patients co-treated with an ACE-inhibitor.

Tricyclic antidepressants/Antipsychotics/Anaesthetics:

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE-inhibitors may result in further reduction of blood pressure (see WARNINGS AND SPECIAL PRECAUTIONS).

Sympathomimetics*:*

Sympathomimetics may reduce the antihypertensive effects of **Vectoryl®**.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE-inhibitor therapy including perindopril.

HUMAN REPRODUCTION:

The use of **Vectoryl®** is contraindicated during pregnancy.

Pregnant women should be informed of the potential hazards to the foetus and must not take **Vectoryl®** during pregnancy (see CONTRAINDICATIONS). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with **Vectoryl®** should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE-inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.

Vectoryl® passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see CONTRAINDICATIONS).

It is not known whether perindopril is excreted into human breast milk. Therefore, the use of **Vectoryl®** is contraindicated during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

Mild to moderate hypertension:

The recommended dosage is 4 mg orally taken in the morning before breakfast, which can be increased to a single daily dose of 8 mg if necessary after one month of treatment. The tablets should be taken before meals. In elderly patients and in cardiac failure, a substantially lower dosage should be used because of impaired clearance.

Insulin and non-insulin dependent diabetics can be treated with the usual doses.

Congestive heart failure:

Treatment should be initiated under close medical supervision. Initial dose of 2 mg orally as a single dose in the morning, which may, in most instances, be increased to 4 mg (once blood pressure acceptability has been demonstrated).

Reduction of risk of cardiovascular events:

In patients with stable coronary artery disease, **Vectoryl®** should be introduced at a dose of 4 mg once daily for two weeks, and then increased to 8 mg once daily, depending on renal function.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (“see table Renal insufficiency for dosage adjustment“)

Concomitant diuretic therapy in hypertension:

Caution is recommended in patients who are currently being treated with diuretics. As the effects of ACE-inhibitors may be potentiated in a situation where hypovolaemia may occur, the diuretic therapy should be discontinued prior to initiation of therapy with **Vectoryl®**. In the case of combination with a diuretic it is not advisable to prescribe a potassium salt or a potassium-sparing agent before the assay of blood potassium, and attention should be paid to possible overdose of the diuretic.

Renal insufficiency:

In patients with renal insufficiency, the dosage of perindopril must be adjusted in relation to the severity of the insufficiency. The following dosages may be recommended:

Creatinine clearance	Recommended dosage
Between 30 and 60 ml/min	2 mg per day
Between 15 and 30 ml/min	2 mg every other day
< 15 ml/min	2 mg on day of dialysis

Perindopril is dialysable (70 ml/min).

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

Hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment.

SIDE EFFECTS:

Summary of safety profile:

The safety profile of perindopril is consistent with the safety profile of ACE-inhibitors:

The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances,

tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritis, rash, muscle cramps, and asthenia.

Tabulated list of adverse reactions:

The following undesirable effects have been observed during clinical trials and/or post-marketing use with perindopril and ranked under the following frequency:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
Blood and the lymphatic System Disorders	Eosinophilia	Uncommon*
	Agranulocytosis or pancytopenia	Very rare
	Haemoglobin decreased and haematocrit decreased	Very rare
	Leucopenia/neutropenia	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see WARNINGS AND SPECIAL PRECAUTIONS)	Very rare
	Thrombocytopenia	Very rare
Metabolism and Nutrition Disorders	Hypoglycaemia (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS)	Uncommon*

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
	Hyperkalaemia, reversible on discontinuation (see WARNINGS AND SPECIAL PRECAUTIONS)	Uncommon*
	Hyponatraemia	Uncommon*
Psychiatric disorders	Mood disturbances	Uncommon
	Sleep disorder	Uncommon
Nervous System disorders	Dizziness	Common
	Headache	Common
	Paraesthesia	Common
	Vertigo	Common
	Somnolence	Uncommon*
	Syncope	Uncommon*
	Confusion	Very rare
Eye Disorders	Visual disturbances	Common
Ear and labyrinth disorders	Tinnitus	Common
Cardiac Disorders	Palpitations	Uncommon*
	Tachycardia	Uncommon*
	Angina pectoris (see WARNINGS AND SPECIAL PRECAUTIONS)	Very rare
	Dysrhythmia	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see WARNINGS AND SPECIAL PRECAUTIONS)	Very rare

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
Vascular Disorders	Hypotension (and effects related to hypotension)	Common
	Vasculitis	Uncommon*
	Stroke possibly secondary to excessive hypotension in high-risk patients (see WARNINGS AND SPECIAL PRECAUTIONS)	Very rare
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common
	Dyspnoea	Common
	Bronchospasm	Uncommon
	Eosinophilic pneumonia	Very rare
	Rhinitis	Very rare
Gastro-intestinal Disorders	Abdominal pain	Common
	Constipation	Common
	Diarrhoea	Common
	Dysgeusia	Common
	Dyspepsia	Common
	Nausea	Common
	Vomiting	Common
	Dry mouth	Uncommon
	Pancreatitis	Very rare
Hepato-biliary Disorders	Hepatitis either cytolytic or cholestatic (see WARNINGS AND SPECIAL PRECAUTIONS)	Very rare
Skin and	Pruritis	Common

MedDRA System Organ Class	Undesirable Effects	Frequency
Subcutaneous Tissue Disorder	Rash	Common
	Urticaria (see WARNINGS AND SPECIAL PRECAUTIONS)	Uncommon
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see WARNINGS AND SPECIAL PRECAUTIONS)	Uncommon
	Photosensitivity reactions	Uncommon*
	Pemphigoid	Uncommon*
	Hyperhidrosis	Uncommon
	Psoriasis aggravation	Rare*
	Erythema multiforme	Very rare
Musculoskeletal And Connective Tissue Disorders	Muscle cramps	Common
	Arthralgia	Uncommon*
	Myalgia	Uncommon*
Renal and Urinary Disorders	Renal insufficiency	Uncommon
	Acute renal failure	Very rare
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon
General Disorder and Administration Site Condition	Asthenia	Common
	Chest pain	Uncommon*
	Malaise	Uncommon*
	Peripheral oedema	Uncommon*
	Pyrexia	Uncommon*
Investigations	Blood urea increased	Uncommon*

MedDRA System Organ Class	Undesirable Effects	Frequency
	Blood creatinine increased	Uncommon*
	Blood bilirubin increased	Rare
	Hepatic enzyme increased	Rare
Injury, poisoning and procedural complications	Fall	Uncommon*

** Frequency calculated from clinical trials for adverse events detected from spontaneous report*

Cases of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) have been reported with other ACE-inhibitors. SIADH can be considered as a very rare, but possible complication associated with ACE-inhibitor therapy including perindopril.

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms associated with overdose of ACE-inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

The recommended treatment of an overdose is an intravenous infusion of normal saline 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. **Vectoryl®** may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously. Expected symptoms and signs would be linked to hypotension. Further treatment is symptomatic and supportive.

IDENTIFICATION:

White rod-shaped tablets and scored on both sides.

PRESENTATION:

In PVC film and aluminium foil blister pack of 30 tablets placed into a carton ~~box~~.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place.

Keep out of reach of children.

REGISTRATION NUMBER:

34/7.1.3/0480

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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