PERINDOPRIL
COVERSYL®

5 mg film-coated tablet ANTIHYPERTENSIVE

PRODUCT DESCRIPTION
Light-green, rod-shaped film-coated tablet engraved with on one face and scored on both edges. The tablet can be divided into equal doses.

FORMULATION
Each film-coated tablet contains 3.395 mg perindopril corresponding to 5 mg of perindopril arginine.
Excipient with known effect: 72.58 mg lactose monohydrate.

PHARMACODYNAMICS / PHARMACOKINETICS

Pharmacodynamics
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*.

Pharmacokinetics
Absorption: After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour. 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.
Distribution: 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.
Elimination: 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.
Special population: 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.

INDICATIONS
This medicine is prescribed in the following indications:
- treatment of arterial hypertension,
- treatment of congestive heart failure,
- for the prevention of stroke recurrence in combination with Indapamide in patients with a history of cerebrovascular disease.
- stable coronary artery disease: Perindopril (Coversyl) reduces the risk of cardiovascular events in patients with coronary artery disease.

DOSAGE AND ADMINISTRATION

Posology
The dose should be individualized according to the patient profile and blood pressure response.

Hypertension
Perindopril (Coversyl) 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 Perindopril (Coversyl); 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 Perindopril (Coversyl).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril (Coversyl) should be initiated with a 2.5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril (Coversyl) 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.

Symptomatic heart failure
It is recommended that Perindopril (Coversyl), 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.
Patients at high risk of symptomatic hypotension *e.g.* patients with salt depletion with or without hyponatremia, patients with hypovolemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril (Coversyl). Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (Coversyl).

Stable coronary artery disease
Perindopril (Coversyl) should be introduced at a dose of 5 mg once daily for two weeks, then increased to 10 mg once daily, depending on renal function and provided that the 5 mg dose is well tolerated.
Elderly patients should receive 2.5 mg once daily for one week, then 5 mg once daily the next week, before increasing the dose up to 10 mg 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.

Special population
Patients with 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
Hemodialyzed patients *	
$Cl_{CR} < 15$	2.5 mg on the day of dialysis

* Dialysis clearance of perindoprilat is 70 ml/min.
For patients on hemodialysis, the dose should be taken after dialysis.

Patients with hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment.

Pediatric population
The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established. Therefore, use in children and adolescents is not recommended.

Method of administration
For oral use.
Perindopril (Coversyl) is recommended to be taken once daily in the morning before a meal.

CONTRAINDICATIONS
- Hypersensitivity to the active substance, 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;
- Concomitant use of Perindopril (Coversyl) with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m²).
- Concomitant use with sacubitril/valsartan therapy. Perindopril (Coversyl) must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces,
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney.

SPECIAL WARNINGS AND PRECAUTIONS
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, diarrhea or vomiting, or who have severe renin-dependent hypertension. 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, hyponatremia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischemic 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 Perindopril (Coversyl). This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril (Coversyl) may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy
As with other ACE inhibitors, Perindopril (Coversyl) 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.

Renal impairment
In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance 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.
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 Perindopril (Coversyl) 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 Perindopril (Coversyl) 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 Perindopril (Coversyl) may be required.

Hemodialysis patients
Anaphylactoid reactions have been reported in patients dialyzed 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 Perindopril (Coversyl) in patients with a recent kidney transplantation.

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. 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, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril (Coversyl). This may occur at any time during therapy. In such cases, Perindopril (Coversyl) 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 edema 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.

Intestinal angioedema has been reported rarely 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. 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. Concomitant use of ACE inhibitors with NEP inhibitors (*e.g.* racecadotril), mTOR inhibitors (*e.g.* sirolimus, everolimus, temsirolimus) and gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (*e.g.* swelling of the airways or tongue, with or without respiratory impairment). Caution should be used when starting racecadotril, mTOR inhibitors (*e.g.* sirolimus, everolimus, temsirolimus) and gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

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 desensitization
Patients receiving ACE inhibitors during desensitization 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.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anemia
Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril 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 perindopril is used in such patients, periodic monitoring of white blood cell counts 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 non-black patients.
As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states 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 inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Perindopril (Coversyl) 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.

Hyperkalemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (*e.g.* spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (*e.g.* heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. 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 arrhythmias. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Diabetic patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with an ACE inhibitor.

Lithium
The combination of lithium and perindopril is generally not recommended.

Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is generally not recommended.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Primary aldosteronism
Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Excipients
Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or total lactase deficiency should not take this medicinal product.

Level of sodium
Perindopril (Coversyl) contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

Lactation
Because no information is available regarding the use of Perindopril (Coversyl) during breastfeeding, Perindopril (Coversyl) is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Fertility
There was no effect on reproductive performance or fertility.

DRIVING AND USING MACHINES
Perindopril (Coversyl) has no direct influence on the ability to drive and use machines 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.

INTERACTIONS
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, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Drugs increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril / valsartan is contraindicated as this increases 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.
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (*e.g.* sirolimus, everolimus, temsirolimus) and gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema.

Drugs inducing hyperkalemia
Although serum potassium usually remains within normal limits, hyperkalemia may occur in some patients treated with Perindopril (Coversyl) 5 mg. Some drugs or therapeutic classes may increase the occurrence of hyperkalemia: aliskiren, potassium salts, potassium-sparing diuretics, (*e.g.* spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and cotrimoxazole (trimethoprim / sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these drugs increases the risk of hyperkalemia. Therefore, the combination of Perindopril (Coversyl) 5 mg with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant use contraindicated
Aliskiren
In diabetic or impaired renal patients, risk of hyperkalemia, 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 hemofiltration 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. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Concomitant use not recommended
Aliskiren
In patients other than diabetic or impaired renal patients, risk of hyperkalemia, 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, hyperkalemia, 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 edema (angioedema).

Potassium-sparing diuretics (*e.g.* triamterene, amiloride,...), potassium (salts)
Hyperkalemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalemic effects).
The combination of perindopril with the above-mentioned drugs is not recommended. If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium 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.

Concomitant use which requires special care
Antidiabetic agents (insulins, oral hypoglycemic agents)
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur 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, the ACE inhibitor 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 hyperkalemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.
Before initiating the combination, check the absence of hyperkalemia and renal impairment.
A close monitoring of the kalemia and creatinemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/day
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (*i.e.* acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening 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.

Concomitant use which requires some care
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.

Tricyclic antidepressants / Antipsychotics / Anesthetics
Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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

ADVERSE DRUG REACTIONS
a. 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, paresthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnea, abdominal pain, constipation, diarrhea, dysgeusia, dyspepsia, nausea, vomiting, pruritus, rash, muscle cramps, and asthenia.

b. 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 (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (< 1/10000); 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
	Hemoglobin decreased and hematocrit decreased	Very rare
	Leucopenia / neutropenia	Very rare
	Hemolytic anemia in patients with a congenital deficiency of G-6PDH	Very rare
	Thrombocytopenia	Very rare
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare
Metabolism and Nutrition Disorders	Hypoglycemia	Uncommon*
	Hyperkalemia, reversible on discontinuation	Uncommon*
	Hyponatremia	Uncommon*
Psychiatric disorders	Depression	Uncommon*
	Mood disturbances	Uncommon
	Sleep disorder	Uncommon
Nervous System disorders	Dizziness	Common
	Headache	Common
	Paresthesia	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	Very rare
	Arrythmia	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high-risk patients	Very rare
Vascular Disorders	Hypotension (and effects related to hypotension)	Common
	Vasculitis	Uncommon*
	Flushing	Rare*
	Stroke possibly secondary to excessive hypotension in high-risk patients	Very rare
	Raynaud's phenomenon	Not known
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common
	Dyspnea	Common
	Bronchospasm	Uncommon
	Eosinophilic pneumonia	Very rare
	Rhinitis	Very rare

MedDRA System Organ Class	Undesirable Effects	Frequency
Gastrointestinal Disorders	Abdominal pain	Common
	Constipation	Common
	Diarrhea	Common
	Dysgeusia	Common
	Dyspepsia	Common
	Nausea	Common
	Vomiting	Common
	Dry mouth	Uncommon
	Pancreatitis	Very rare
Hepato-biliary Disorders	Hepatitis either cytolitic or cholestatic	Very rare
Skin and Subcutaneous Tissue Disorders	Pruritus	Common
	Rash	Common
	Urticaria	Uncommon
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx	Uncommon
	Photosensitivity reactions	Uncommon*
	Pemphigoid	Uncommon*
	Hyperhydrosis	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	Rare
	Anuria / Oliguria	Rare*
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon
General Disorders and Administration Site Condition	Asthenia	Common
	Chest pain	Uncommon*
	Malaise	Uncommon*
	Edema peripheral	Uncommon*
	Pyrexia	Uncommon*
Investigations	Blood urea increased	Uncommon*
	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*

REPORTING OF ADVERSE DRUG REACTION
For suspected adverse drug reaction, report to the FDA at ***www.fda.gov.ph***
Seek medical attention immediately at the first sign of any adverse drug reaction.

OVERDOSE AND TREATMENT
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 hemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

MISSED DOSE
The patient should take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

DISCONTINUATION OF TREATMENT
As the treatment with Perindopril (Coversyl) is usually life-long, patient should discuss with the doctor before stopping this medicinal product.

PACKAGING
White polypropylene tablet container equipped with a polyethylene flow reducer and a white opaque stopper containing a desiccant gel.
Box of 30 tablets.

STORAGE CONDITIONS
Keep the container tightly closed in order to protect from moisture. Store at temperatures not exceeding 30°C.
Keep out of reach and sight of children.

Do not use this drug after the expiry date printed on the box.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Les Laboratoires Servier – France

Manufactured by:
Les Laboratoires Servier Industrie
905 Route de Saran, 45520 Gidy – France

Imported by:
SERVIER PHILIPPINES, INC.
Unit AD, 11F, 8 Rockwell, Hidalgo Drive,
Rockwell Center, Brgy. Poblacion,
Makati, Metro Manila

Distributed by:
Zuellig Pharma Corporation
Km. 14 West Service Road,
South Super Highway cor. Edison Ave.,
Sun Valley, Parañaque City

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