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Perinace

TABLET PERINDOPRIL ERBUMINE

DESCRIPTION & COMPOSITION

Perinace Tablet 4mg
An oblong shape, scored, white to off-white tablet
Each tablet contains 4 mg of perindopril erbumine.

Perinace Tablet 8mg
A white oval biconvex shape tablet, plain on one side and score line on the other side.
The tablet can be divided into equal halves.
Each tablet contains 8 mg of perindopril erbumine.

PHARMACODYNAMICS
Pharmacotherapeutic group: ACE inhibitor, plain, ATC code: C09A A04

Mechanism of action
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.

Clinical efficacy and safety
Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.
Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.
Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.
Discontinuation of treatment does not lead to a rebound effect.
Perindopril reduces left ventricular hypertrophy.
In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.
An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure:
Perindopril reduces cardiac work by a decrease in pre-load and after-load.
Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of perindopril erbumine. to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

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. 27% 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 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 populations
Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

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

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required *(see DOSAGE AND ADMINISTRATION, WARNING(S) AND PRECAUTION(S))*

INDICATION(S)
Hypertension:
Treatment of hypertension.

Heart failure:
Treatment of symptomatic heart failure.

Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

RECOMMENDED DOSAGE
The dose should be individualised according to the patient profile *(see WARNING(s) AND PRECAUTION(s))* and blood pressure response.

Hypertension:
Perinace may be used in monotherapy or in combination with other classes of antihypertensive therapy *(see CONTRAINDICATIONS, DRUG INTERACTIONS, WARNING(s) AND PRECAUTION(s) and PHARMACODYNAMICS).*
The recommended starting dose is 4 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 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with Perinace; 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 Perinace *(see WARNING(s) AND PRECAUTION(s)).*
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perinace should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perinace 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 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary, depending on renal function (see table below).

Symptomatic heart failure:
It is recommended that Perinace, 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 mg taken in the morning. This dose may be increased after 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision *(see WARNING(s) AND PRECAUTION(s)).*

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

Stable coronary artery disease:
Perinace should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.

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 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
$Cl_{cr} \geq 60$	4 mg per day
$30 < Cl_{cr} < 60$	2 mg per day
$15 < Cl_{cr} < 30$	2 mg every other day
Haemodialysed patients *	
$Cl_{cr} < 15$	2 mg on the day of dialysis

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

Patients with hepatic impairment:
No dosage adjustment is necessary in patients with hepatic impairment *(see WARNING(s) AND PRECAUTION(s) and PHARMACOKINETICS).*

Paediatric 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:
Perinace is recommended to be taken once daily in the morning before a meal.

ROUTE OF ADMINISTRATION: Oral

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 *(see WARNING(s) AND PRECAUTION(s));*
- Hereditary or idiopathic angioedema;
- Second and third trimesters of pregnancy *(see WARNING(s) AND PRECAUTION(s) and USE IN PREGNANCY AND LACTATION);*
- Concomitant use of Perinace with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) *(see DRUG INTERACTIONS and PHARMACODYNAMICS);*
- Concomitant use with sacubitril/valsartan *(see WARNING(s) AND PRECAUTION(s) and DRUG INTERACTIONS);*
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces *(see DRUG INTERACTIONS);*
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney *(see WARNING(s) AND PRECAUTION(s).*

WARNINGS AND PRECAUTIONS
INCREASED RISK OF BIRTH DEFECTS, FETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY

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

Hypotension
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension *(see DRUG 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 at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored *(see DOSAGE AND ADMINISTRATION and 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 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 Perinace.
This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perinace may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, Perinace 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 *(see DOSAGE AND ADMINISTRATION)* and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients *(see 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, 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 Perinace 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 Perinace 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 Perinace may be required.

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

Kidney transplantation
There is no experience regarding the administration of Perinace in patients with a recent kidney transplantation.

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with 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, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perinace *(see SIDE EFFECTS).* This may occur at any time during therapy.
In such cases, Perinace should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor *(see CONTRAINDICATIONS).*
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 *(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 DRUG INTERACTIONS and SIDE EFFECTS).* Concomitant use of other NEP inhibitors (e.g., racecadotril) and ACE inhibitors may also increase the risk of angioedema *(see DRUG 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 DRUG INTERACTIONS).*

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

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

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up *(see 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 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/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perinace 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 ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia 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).
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. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium *(see DRUG INTERACTIONS).*

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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 an ACE inhibitor *(see DRUG INTERACTIONS)*.

Lithium:
The combination of lithium and perindopril is generally not recommended *(see DRUG INTERACTIONS)*.

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 *(see DRUG INTERACTIONS)*.

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, hyperkalaemia 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 *(see DRUG INTERACTIONS, and PHARMACODYNAMICS)*.
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 *(see CONTRAINDICATIONS and USE IN PREGNANCY AND LACTATION)*;

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

INTERACTIONS WITH OTHERS MEDICAMENTS
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 (including acute renal failure) compared to the use of a single RAAS-acting agent *(see CONTRAINDICATIONS, WARNING(S) AND PRECAUTION(S) and PHARMACODYNAMICS)*.

Drugs inducing hyperkalaemia
Some drugs 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 drugs increases the risk of hyperkalaemia.

Concomitant use contra-indicated (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., polyacrylonitrile membranes) and low-density lipoprotein apheresis with dextran sulfate 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 CONTRAINDICATIONS) and WARNING(s) AND PRECAUTION(s))*.

Concomitant use not recommended (see WARNING(s) AND PRECAUTION(s)) :
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 WARNING(s) AND PRECAUTION(s))*.

Potassium-sparing diuretics (e.g., triamterene, amiloride ,) potassium salts:
Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects).
The combination of perindopril with the above-mentioned drugs is not recommended *(see WARNING(s) AND PRECAUTION(s))*.
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 *(see WARNING(s) AND PRECAUTION(s))*.

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

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 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.
A close monitoring of the kalaemia and creatininaemia 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 aspirin ≥ 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.

Racecadotril
ACE inhibitors (e.g., perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a drug 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 WARNING(s) AND PRECAUTION(s))*.

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.

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin):
Increased risk of angioedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin, in patients co-treated with an ACE inhibitor.

Tricyclic antidepressants/Antipsychotics/Anaesthetics:
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure *(see WARNING(s) AND PRECAUTION(s))*.

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.

USE IN PREGNANCY AND LACTATION
Pregnancy:

> **The use of ACE inhibitors is not recommended during the first trimester of pregnancy *(see WARNING(s) AND PRECAUTION(s))*.**
>
> **The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy *(see CONTRAINDICATIONS) and WARNING(s) AND PRECAUTION(s))*. When pregnancy is detected, this drug should be discontinued as soon as possible.**

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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). 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 *(see CONTRAINDICATIONS) and WARNING(s) AND PRECAUTION(s))*.

Lactation:
Because no information is available regarding the use of Perinace during breast-feeding, Perinace is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility:
There was no effect on reproductive performance or fertility.

SIDE EFFECTS/ADVERSE 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, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritus, rash, muscle cramps, and asthenia.

Tabulated list of adverse reactions by frequency and system organ class (SOC)

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
	Leucopoenia/neutropenia	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G6PDH	Very rare
	Thrombocytopenia	Very rare
Metabolism and Nutrition Disorders	Hypoglycaemia	Uncommon*
	Hyperkalaemia, reversible on discontinuation	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	Very rare
	Arrhythmia	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*
	Stroke possibly secondary to excessive hypotension in high -	Very rare
	Raynaud's phenomenon	Not known
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	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*
	Psoriasis aggravation	Rare*
	Hyperhidrosis	Uncommon*
	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 Disorders and Administration Site Condition	Asthenia	Common
	Chest pain	Uncommon*
	Malaise	Uncommon*
	Oedema 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*

Cases of 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.

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

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Perinace 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.

STORAGE CONDITIONS
Store in a dry place below 30°C.
Keep out of reach of children. Jauhkan daripada kanak-kanak.

SHELF LIFE
• Shelf life: Please refer to outerbox

PACKING/ PACK SIZES
Foil blisters of 3 x 10's and 10 x 10's tablets packed in an aluminium pouch per unit box with a package insert.
All pack sizes may not be marketed.

PRODUCT REGISTRATION HOLDER
Duopharma Manufacturing (Bangi) Sdn. Bhd.
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