PREXUM 4 mg

Perindopril

COMPOSITION

Each captab contains perindopril tert-butylamine salt 4 mg.

INDICATIONS

- Hypertension
- Heart failure
  In congestive heart failure, PREXUM is used as an adjunct to diuretic and digitalis.
  Therapy must be under supervision of physician.
- Reduction of stroke recurrence in combination with indapamide in patients with a history of cerebrovascular disease.
- Stable coronary artery disease
  Treatment of stable coronary artery disease in patients with a history of post myocardial infarction and/or revascularisation.
  PREXUM should be used with standard treatment for management of coronary artery disease

POSOLOGY

- Hypertension

  PREXUM may be used in monotherapy or in combination with other classes of antihypertensive therapy.
  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 PREXUM; 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 PREXUM (see "Warnings and precautions").
  In hypertensive patients in whom diuretic can not discontinued, therapy with PREXUM should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of PREXUM 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 8 mg if necessary depending on renal function (see table below).

- Heart failure

  It is recommended that PREXUM, 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 by increments of 2 mg at intervals of no less than 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 "Warnings and precautions").
  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 PREXUM. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with PREXUM (see "Warnings and precautions").

- Reduction of stroke recurrence

  In patients with a history of cerebrovascular disease, PREXUM should be introduced at a dose of 2 mg daily for two weeks, then increased to 4 mg daily for a further 2 weeks before introducing indapamide.
  Treatment can be initiated at any time from 2 weeks up to several years after the initial stroke episode.

- Stable coronary artery disease

  PREXUM 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.

Dosage adjustment in renal impairment

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

Table 1 : dosage adjustment in renal impairment

Creatinine clearance (ml/min)	Recommended dose
$Cl_{CR} \geq 60$	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.

Dosage adjustment in hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment (see "Warnings and precautions" and "Pharmacokinetic properties")

Paediatric use

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

CONTRAINDICATIONS

- Hypersensitivity to perindopril, to any of the excipients or to any other ACE inhibitor;
- History of angioedema associated with previous ACE inhibitor therapy;
- Hereditary or idiopathic angioedema;
- Second and third trimesters of pregnancy (see "Warnings and precautions, Pregnancy").

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, 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 "Posology" 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 normal saline. 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 PREXUM. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of PREXUM may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, PREXUM 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 "Posology") 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 PREXUM 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 PREXUM 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 PREXUM 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 PREXUM in patients with a recent kidney transplantation.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including PREXUM (see "Side effects"). This may occur at any time during therapy. In such cases, PREXUM 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 havebeen 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.
Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
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").

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

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

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

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 nonproductive, 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, PREXUM 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. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the abovementioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

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. Antidiabetic agents".)

Lithium
The combination of lithium and perindopril is generally not recommended (see "Drug interactions").

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see "Drug interactions").

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

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

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see "Preclinical safety data").

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

Lactation
It is not known whether perindopril is excreted into human breast milk. Therefore the use of PREXUM is not recommended in women who are breast-feeding.

Due to the presence of lactose, this medicine should not be used in the case of congenital galactosaemia, glucose and galactose malabsorption syndrome or a deficit in lactase.

Effects 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

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

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin 3 ≥ g/day
The administration of a non-steroidal anti-inflammatory drugs may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.

Antihypertensive agents and vasodilators
Concomitant use of these agents may increase the hypotensive effects of perindopril.

Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

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

Tricyclic antidepressants/Antipsychotics/Anesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see "Warnings and precautions").

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

SIDE EFFECTS
The following side effects have been observed during treatment with perindopril and ranked under the following frequency.

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

Psychiatric disorders:
Uncommon: mood or sleep disturbances

Nervous system disorders:
Common: headache, dizziness, vertigo, paresthaesia
Very rare: confusion

Eye disorders:
Common: vision disturbance

Ear and labyrinth disorders:
Common: tinnitus

Cardio-vascular disorders:
Common: hypotension and effects related to hypotension
Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to

excessive hypotension in high risk patients (see "Warnings and precautions").

Respiratory, thoracic and mediastinal disorders:
Common: cough, dyspnoea
Uncommon: bronchospasm
Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:
Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation
Uncommon: dry mouth
Very rare: pancreatitis

Hepato-biliary disorders:
Very rare: hepatitis either cytolytic or cholestatic (see "Warnings and precautions").

Skin and subcutaneous tissue disorders:
Common: rash, pruritus
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see "Warnings and precautions").
Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Uncommon: renal insufficiency
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: impotence

General disorders:
Common: asthenia
Uncommon: sweating

Blood and the lymphatic system disorders:
Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see "Warnings and precautions").

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

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

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 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. Perindopril may be removed from the general circulation by haemodialysis. (See "Warnings and precautions, Haemodialysis Patients.") Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ANGIOTENSIN CONVERTING ENZYME INHIBITOR
ATC code: C09A A04

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

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

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure
PREXUM 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 PREXUM to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with history of cerebrovascular disease :
A multicentric, international, double-blind, randomised, placebo-controlled study (PROGRESS) has evaluated the benefits of a 4 years' treatment with an active treatment (perindopril, either alone or in combination with diuretuc indampamide) on the risk of stroke recurrence in patients with a history of cerebrovascular disease.

The primary outcome was stroke.

After a run-in period of perindopril 2 mg for two weeks once daily then 4 mg once daily for two further weeks, 6105 patients were randomised to placebo (n = 3054) or perindopril 4 mg either alone or in combination with indapamide (n = 3051). Indapamide was combined unless patients had definite indication or contraindication to a diuretic.
These treatments were prescribed in addition to conventional therapies for stroke ad/or hypertension or any other pathological condition.

All randomised patients had a history of cerebrovascular disease (stroke or transient ischemic attack) within the past 5 years. There were no blood pressure entry criteria : 2916 patients were hypertensive

and 3189 were normotensive.

After a mean duration of follow-up of 3.9 years, blood pressure (systolic/diastolic) was reduced by average of 9.0/4.0 mmHg and a significant reduction of 28% (95% CI [17; 38], p < 0.0001) in the risk of stroke recurrence (both ischaemic and haemorragic) was observed in treated patients compared to placebo (10.1% vs 13.8%).

In addition, significant overall reductions were observed in the risk of :
- fatal or disabling stroke (4.0% vs 5.9% corresponding to 33% risk reduction)
- total major cardiovascular events composite of cerebrovascular death, non fatal myocardial infarction and non fatal stroke (15.0% vs 19.8% corresponding to 26% risk reduction)
- stroke-related dementia (1.4% vs 2.1% corresponding to 34% risk reduction) and stroke-related severe cognitive decline (1.6% vs 2.8% corresponding to 45% risk reduction)
- major coronary artery diseases including non fatal myocardial infarction or coronary artery disease deaths (3.8% vs 5.0% corresponding to 26% risk reduction)

These therapeutic benefits were observed irrespective of whether patients were hypertensive or normotensive, and irrespective of age, gender, stroke subtype or presence of diabetes.

The PROGRESS results have shown that treatment for 5 years would result in the avoidance of one stroke among every 23 patients and one major cardiovascular event among every 18 patients.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n = 6110) or placebo (n = 6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall. 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

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

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

Pharmacokinetic properties
After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

About 20 % of the total quantity of perindopril absorbed is converted into perindoprilat. the active metabolite. In addition to active perindoprilat. perindopril yields five metabolites, all inactive. The plasma half-life of perindopril is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

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

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30 %), but is concentration dependent.

Perindoprilat is eliminated in the urine and the half-life of the unbound fraction is approximately 3 to 5 hours. Dissociation of perindoprilat bound to angiotensin converting enzyme leads to an "effective" elimination half-life of 25 hours, resulting in steady-state within 4 days.

After repeated administration, no accumulation of perindopril is observed. 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 also "Posology" and "Warnings and precautions").

Preclinical safety data

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

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

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

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

STORAGE CONDITION
Store at 25°C-30°C.
Shelf life : 2 years

PACKING
Box of 1 blister of 30 captabs

Reg. No.: DKL0920719104A1

ON PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

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