SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM

ACTI-PREX™ 4 mg TABLETS

COMPOSITION

Each tablet contains Perindopril tert-butylamine (salt) 4 mg, (equivalent to 3.34 mg of Perindopril). Contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Vascular medicines. Other hypotensives.

PHARMACOLOGICAL ACTION

Perindopril is an angiotensin converting enzyme (ACE) inhibitor, which is a pro-drug for perindoprilat, which inhibits ACE in human subjects and animals. The mechanism through which perindoprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyses conversion of the inactive decapeptide, angiotensin I, to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor, which stimulates aldosterone secretion by the adrenal cortex, and provides negative feedback on renin secretion. Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and may be associated with a small increase of serum potassium.

After administration of perindopril, ACE is inhibited in a dose and blood concentration-related fashion, with maximal inhibition of 80 to 90 % attained by 8 mg persisting for 10 to 12 hours. Twenty four hour ACE inhibition is about 60 % after these doses. The degree of ACE inhibition achieved by a given dose appears to diminish over time (the ID50 increases). The pressor response to an angiotensin I infusion is reduced by perindopril, but this effect is not as persistent as the effect on ACE; there is about 35 % inhibition at 24 hours after a 12 mg dose.

Pharmacokinetics

After oral administration, the absorption of perindopril is rapid and the peak plasma levels of 4 µg/l occur one hour following a 4 mg dose. 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, **Acti-Prex™** 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.

INDICATIONS

Acti-Prex™ is indicated for the treatment of mild to moderate hypertension.

Congestive heart failure not adequately controlled by conventional therapy with diuretics and digitalis and in whom vasodilatation is indicated.

CONTRA-INDICATIONS

- Sensitivity to any of the components of **Acti-Prex™**.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARB's): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Moderate to severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- Thiazide diuretics in (fixed dose) combination with **Acti-Prex™** should not be given to patients with Addison's disease. This therapy is also contra-indicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.

- Lithium therapy: Concomitant administration with **Acti-Prex™** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS

Hypotension: ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting or have severe renin-dependent hypertension. Symptomatic hypotension has been observed in patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment.

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 incident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with **Acti-Prex™.** This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of **Acti-Prex™** may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy: (see **CONTRA-INDICATIONS**)

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. Potassium and creatinine should be routinely monitored for these patients.

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.

Surgery/Anaesthesia: In patients undergoing surgery or during anaesthesia with agents that produce hypotension, **Acti-Prex™** 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 **Acti-Prex™.** Patients at risk 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 above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic patients: 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.

Effects on ability to drive and use machines: When driving or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

Kidney transplantation: There is no experience regarding the administration of **Acti-Prex™** in patients with 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 **Acti-Prex™.** This may occur at any time during therapy. In such cases, **Acti-Prex™** 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. When 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 patient 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.

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

Anaphylactoid 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 (**SIDE-EFFECTS**).

Neutropenial Agranulocytosis/Thrombocytopenia/Anaemia: Neutropenial agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving **Acti-Prex™.** In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. **Acti-Prex™** 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 **Acti-Prex™** 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.

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.

Race: ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, **Acti-Prex™** 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.

Lithium: The combination of lithium and **Acti-Prex™** is generally not recommended.

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes: The combination of **Acti-Prex™** and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended.

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: 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. Use with caution and with frequent monitoring of serum potassium, if concomitant use is indicated because of demonstrated hypokalaemia.

Lithium: Increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with **Acti-Prex™** (see **CONTRA-INDICATIONS**). Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors.

Non-steroidal anti-inflammatory drugs (NSAID's), including aspirin > 3 g/day: NSAID's may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAID's and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. The effects are usually reversible. Acute renal failure may rarely 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 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/Anaesthetics: Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.

Sympathomimetics: These may reduce the antihypertensive effects of ACE inhibitors.

PREGNANCY AND LACTATION

Safety during pregnancy and lactation has not been established.

Pregnancy**:** **Acti-Prex™** 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.

Acti-Prex™ is contra-indicated 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). Should exposure to **Acti-Prex™** 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 **Acti-Prex™** is not recommended in women who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

Mild to moderate hypertension: The recommended dosage is 2 mg or 4 mg orally taken in the morning before breakfast which can be increased to a single dose of 8 mg if necessary after one month of treatment. The tablets should be taken before meals.

In elderly patients and in cardiac failure, substantially lower dosage should be used because of impaired clearance. Insulin and non-insulin dependent diabetics can be treated with the usual dose.

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

Concomitant diuretic therapy in hypertension: Caution is recommended in patients who are currently being treated with diuretics. As the effects of ACE inhibitors may be potentiated in a situation where hypovolaemia may occur, the diuretic therapy should be discontinued prior to initiation of therapy with **Acti-Prex™.**

In case of a combination with a diuretic it is not advisable to prescribe a potassium salt or a potassium-sparing agent before assay of blood potassium, and attention should be paid to possible overdosage of the diuretic.

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

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

Perindopril is dialysable (70 ml/min)

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

The following side-effects have been observed during treatment with perindopril

Frequent

Nervous system disorders: Headache, dizziness, vertigo, paresthaesia

Eye disorders: Vision disturbance

Ear and labyrinth disorders: Tinnitus

Cardiovascular disorders: Hypotension and effects related to hypotension

Respiratory, thoracic and mediastinal disorders: Cough, dyspnoea

Gastrointestinal disorders: Nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation

Skin and subcutaneous tissue disorders: Rash, pruritus

Musculoskeletal, connective tissue and bone disorders: Muscle cramps

General disorders: Aesthesia

Less Frequent

Psychiatric disorders: Mood or sleep disturbances

Respiratory, thoracic and mediastinal disorders: Bronchospasm

Gastrointestinal disorders: Dry mouth

Skin and subcutaneous tissue disorders: Angioedema of the face, extremities, lips, mucous membrane, tongue, glottis and/or larynx, urticaria

Renal and urinary disorders: Renal insufficiency

Reproductive system and breast disorders: Impotence

General disorders: Sweating

Very Rare

Nervous system disorders: Confusion

Cardiovascular disorders: Arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients

Respiratory, thoracic and mediastinal disorders: Eosinophilic pneumonia, rhinitis

Gastrointestinal disorders: Pancreatitis

Hepato-biliary disorders: Hepatitis either cytolytic or otherwise

Skin and subcutaneous tissue disorders: Erythema multiforme

Renal and urinary disorders: Acute renal failure

Blood and the lymphatic system disorders: Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia and cases of agranulocytosis or pancytopenia, haemolytic anaemia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Expected symptoms and signs would be linked to hypotension. Apart from gastric washout, the setting up of an intravenous line for the infusion of isotonic saline solution is recommended. Perindopril is dialysable (70 ml/min). Further treatment is symptomatic and supportive.

Limited data is 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. **Acti-Prex™** may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

IDENTIFICATION

White oblong tablets scored on both edges having ‘PP' debossed on one side and ‘4' on the other.

PRESENTATION

Acti-Prex™ are available in Polypropylene bottles containing 28, 30 and 500 tablets and HDPE bottles containing 28 and 30 tablets.

Acti-Prex™ are also available in Aluminium/Aluminium blister containing 30 tablets

STORAGE INSTRUCTIONS

Store at or below 25 ^{O}C in a dry place. Protect from light.

Keep blister in carton until required for use

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

41/7.1.3/0175

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

02 July 2014

PER/PI/C