Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ByZestra 2.5 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.5 mg of lisinopril (as dihydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White, oval tablets, marked ‘LSN 2.5’ on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Arterial hypertension
  It may be used alone or concomitantly with other classes of antihypertensive agents, e.g. thiazide diuretics.

- Treatment of heart failure as additive therapy to non-potassium-sparing diuretics and where appropriate, digitalis.

- Treatment of acute myocardial infarction, in haemodynamically stable patients (systolic blood pressure >100 mm Hg) without significant renal dysfunction (serum creatinine <177 micromol/l [2.0 mg/dl] and proteinuria <500 mg/24 hours.) Lisinopril should be given in addition to usual standard therapy in MI (thrombolytics, acetylsalicylic acid and ß blocking agents), especially together with nitrates.

- Renal Complications of Diabetes Mellitus
  Treatment of renal disease in hypertensive patients with type 2 daibetes mellitus and incipient nephropathy.

4.2 Posology and method of administration

Precautionary note:
Excessive first dose hypotension may occur in high risk patients (in patients with salt and/or fluid deficiency, e.g. after dialysis, vomiting, in concomitant diuretic therapy, in patients with heart failure, severe or renal hypertension). Initiation of therapy requires, if possible, correction in salt and/or body fluids deficiencies, discontinuation or reduction of an existing diuretic therapy for two to three days before starting ACE inhibition and starting therapy with the lowest single dose of 2.5mg lisinopril in the morning.

Patients at high risk for severe acute hypotension should be monitored medically preferably in hospital, for as long as its maximal effect is expected (generally for at least 8 hours) after administration of the first dose and whenever the dose of ACE inhibitors and/or diuretic is increased. This also applies to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

In patients with malignant hypertension or severe cardiac insufficiency initiation of therapy and dose adjustment should be performed in a hospital.

Unless prescribed otherwise, the following dosage regimen is recommended:
Arterial hypertension
Treatment should be initiated with 5-10mg in the morning.
The dose should be titrated to give the optimum control of blood pressure. The time interval between dose increases should not be less than 3 weeks.
The usual maintenance dose is 20mg lisinopril once daily, but doses up to 80mg once daily may be used.

A lower initial dose (2.5mg lisinopril in the morning) will be necessary at renal impairment, at heart failure, in patients who do not tolerate discontinuation if diuretic treatment, in patients who are volume and/or salt depleted (e.g. after vomiting, diarrhoea or diuretic therapy), in patients with severe or renovascular hypertension and in elderly patients.

Heart failure
Lisinopril can be given in addition to existing therapy with diuretics and digitalis.
The initial dose is 2.5mg lisinopril in the morning. The maintenance dose should be titrated in increments of 2.5mg lisinopril at intervals of two to four weeks.
Dose increases must be gradual and reflect individual patient response to therapy.
The usual maintenance dose is 5-20mg once daily. The maximum dose of 35mg lisinopril per day should not be exceeded.

Acute myocardial infarction in haemodynamically stable patients
Lisinopril should be given as a supplement to the usual standard therapy in MI. Treatment with lisinopril may be initiated within 24 hours of symptom onset provided that the patients are haemodynamically stable. The initial dose is 5 mg lisinopril and then 5 mg after 24 hours, 10 mg after 48 hours and thereafter 10 mg once daily. Patients with a low systolic blood pressure (120 mmHg or less) at the start of treatment or during the first 3 days following the infarction should be given a lower dose - 2.5 mg orally (*see section 4.4*).
In case of hypotension occurs (systolic blood pressure lower than 100 mmHg), a daily maintenance dose of 5 mg should not be exceeded, with reduction to 2.5 mg if necessary. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) despite of a dose reduction to 2.5mg lisinopril per day, lisinopril should be discontinued.

The treatment should be continued for 6 weeks. The minimal maintenance dose is 5mg lisinopril per day. Patients with symptoms of cardiac insufficiency should continue treatment with lisinopril
Lisinopril is compatible with intravenous or transdermal administration of glyceryl trinitrate.

Dosage in moderate renal impairment
If the creatinine clearance is 30-70ml/min respectively, and in elderly patients (over 65 years):
The initial dose is 2.5mg lisinopril in the morning, the maintenance dose is usually 5-10mg lisinopril per day according to blood pressure control. The maximum dose of 20mg lisinopril per day should not be exceeded.

It is recommended discontinuing administration of diuretics 2 or 3 days before initiation of therapy with lisinopril. The possibility of hypotensive effects with lisinopril can be minimised by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril.

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

Renal complications of diabetes mellitus
In hypertensive patients with type 2 diabetes mellitus, the dose is 10mg lisinopril once daily which should be increased to 20mg once daily, if necessary, to achieve a sitting blood pressure below 90mm Hg.

Lisinopril can be taken independently from meals, but should be taken with a sufficient amount of liquid.
Lisinopril should be administered once daily.

Place the ByZestra snaptab on a hard surface with the centre groove facing upward. Exert pressure from the top with your thumb and the snaptab will break into two equal pieces.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients or other ACE inhibitors.
- History of angioneurotic oedema related to previous ACE-inhibitor treatment and hereditary/idiopathic angioneurotic oedema (see section 4.4)
- Severe renal impairment (creatinine clearance <30ml/min)
- Haemodynamically relevant aortic or mitral valve stenosis ot hypertrophic cardiomyopathy
- In haemodynamically unstable patients after acute myocardial infarction
- Systolic blood pressure ≤ 100 mmHg before initiation of the treatment with lisinopril
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Concurrent use of lisinopril and poly (acrylonitrile, sodium-2-methylallyl-sulphonate) highflux membranes for emergency dialysis bears the risk of anaphylactic reactions (hypersensitivity reactions to the point if shock). This combination must therefore be avoided either by using other drugs (but not ACE inhibitor) for the treatment of hypertension and/or heart failure, or by using other membrane for dialysis (see section 4.4).
- Cardiogenic shock

4.4 Special warnings and precautions for use

Patients on multiple or high dose diuretics (>80mg of frusemide) with hypovolaemia, hypontraemia (serum sodium <130 mmol/l) pre-existing hypotension, unstable cardiac failure, renal impairment, high-dose vasodilator therapy and patients age 70 years or over are recommended to have lisinopril therapy initiated in hospital.

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 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 (see sections 4.3 and 4.6).

Hypotension
Lisinopril may cause a profound fall in blood pressure especially after the first dose.
Symptomatic hypotension is rare in uncomplicated hypertensive patients. It is more likely to occur in patients who have been electrolyte- or vole-depleted by diuretic, dietary salt restriction, dialysis, diarrhoea or vomiting. It has been reported mainly in patients with severe heart failure with or without associated renal insufficiency. This is more likely in patients on high doses of loop diuretics, or those with hyponatreamia or functional renal impairment. In these patients treatment should be started under close medicinal supervision preferably in hospital, with low doses and careful dose titration with simultaneous control of renal function as well as serum potassium levels. If possible, diuretic treatment should be discontinued temporarily. Such considerations apply also to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.
If hypotension develops the patient should be placed in supine position and volume repletion with oral or intravenous fluids may be required. Atropine may be necessary for treatment of associated bradycardia.
The appearance of hypotension after initial dose does not preclude subsequent careful dose titration with medicinal product after effective treatment. If non-acute hypotension in patients with heart failure becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or lisinopril may become necessary.
If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of lisinopril.

Hypotension in acute myocardial infarction
Treatment with lisinopril must not be initiated in acute myocardial infarction patients if there is a risk of additional serious haemodynamic exacerbation following treatment with a vasodilator. These are patients with a systolic blood pressure of 100 mmHg or lower or with cardiogenic shock. The maintenance dose should be reduced to 5mg or temporarily to 2.5mg, in case the systolic blood pressure is 100 mmHg or lower. Treatment with lisinopril in acute myocardial infarction patients may lead to severe hypotension. In persisting hypotension (systolic blood pressure < 90 mmHg for more than 1 hour), lisinopril should be discontinued.

In patients with severe heart failure following an acute myocardial infarction lisinopril should only be administered if the patient is haemodynamically stable.

Renovascular hypertension / Renal artery stenosis
There is an increased risk for severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with lisinopril. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued and renal function monitored during the first weeks of therapy.

Impaired renal function
In patients with severe renal failure (creatinine clearance < 30 ml/min) the use of lisinopril is contra-indicated (*see section 4.3*).
Lisinopril should be used with caution in patients with renal insufficiency who may require reduced or less frequent doses (*see section 4.2*).

Changes in renal function may be anticipated in susceptible individuals due to the inhibition of the renin-angiotensin-aldosterone system. Close monitoring of the renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. Renal failure has been reported in association with lisinopril mainly in patients with severe heart failure or underlying renal disease including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with lisinopril treatment is usually reversible.
Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when lisinopril has been given concurrently with a diuretic. This situation should lead to reduction of dose/discontinuation of lisinopril/diuretics and raise the possibility of underlying renal artery stenosis.
In acute myocardial infarction treatment with lisinopril should not be initiated in patients with signs of renal impairment, defined as a serum creatinine concentration ≥ 177 micromol/l (2.0 mg/dl) and/or proteinuria above 500 mg/day. If renal impairment develops during treatment with lisinopril (serum creatinine clearance < 30 ml/min, or a doubling of pre-treatment creatinine value), lisinopril must be discontinued.

There is limited experience of lisinopril in renal transplant recipients. Treatment with lisinopril is therefore generally not recommended for the category of patients.

Haemodialysis
In patients in permanent haemodialysis the use of lisinopril is contra-indicated (*see section 4.3,*).

Concomitant application of lisinopril and poly(acrylonitrile, sodium-2-methylallyl-sulphonate) high-flux membranes during dialysis or haemofiltration carries a risk of anaphylactic reactions (hypersensitivity reactions up to anaphylactic shock). First indications of this anaphylaxis are swelling of the face, redness, hypotension and dyspnea within few minutes of commencing haemodialysis. It is recommended to use an alternative membrane in dialysis or an alternative antihypertensive drug in the treatment of hypertension on heart failure (*see section 4.3*).

Hyperkalemia
Hyperkalemia may occur during treatment with lisinopril, especially in the presence of renal insufficiency and/or heart failure. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in serum potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Primary hyperaldesteronism
Patients with primary hyperaldesteronism generally do not respond to antihypertensives with a mode of action based on inhibition of the renin-angiotensin-system. The use of lisinopril is, therefore, not recommended.

Proteinuria
In patients with existing renal function impairment or on relatively high doses of lisinopril rarely proteinuria may occur. In patients with clinically relevant proteinuria (more than 1 g/day) lisinopril should be given after very critical assessment of the risk versus benefit and with regular monitoring of clinical and laboratory parameters.

Elderly
Some elderly patients may be more responsive to an ACE inhibitor than younger patients. In patients older than 65 years administration of low initial doses (2.5mg lisinopril) and monitoring of blood pressure, evaluation of renal function and/or representative laboratory parameters in the initial phase of therapy is recommended.

LDL-lipid apheresis / Desensitisation therapy
During LDL (low-density lipoprotein) apheresis with dextran sulphate, life-threatening anaphylactic reactions may occur when ACE-inhibitor is administered.

Life-threatening anaphylactic reactions (e.g. blood pressure decrease, breathlessness, vomiting, allergic skin reactions) may also occur during desensitisation therapy for insect venom (e.g. bee, wasp stings) and concurrent use of lisinopril. If LDL apheresis or desensitisation therapy for insect venom is necessary, lisinopril should be temporarily replaced by different drugs (other ACE inhibitors excluded) for hypertension or heart failure.

Angioneurotic oedema (*see section 4.3*)
Angioneurotic oedema of the face , extremities, lips mucous membranes, tongue, glottis and/or larynx rarely have been reported in patients treated with ACE-inhibitors including lisinopril which especially occurs during the first weeks of treatment. However, in rare cases angioedema may develop after long-term treatment with an ACE-inhibitor. In such cases, lisinopril therapy should be discontinued promptly and an appropriate monitoring of the patient has to be instituted.

In cases where swelling has been confined to the face and lips, the condition generally resolves without treatment although antihistamines have been useful in relieving symptoms. Patients with a known history of angioedema unrelated to ACE-inhibitor therapy may have an increased risk for developing angioedema after taking an ACE-inhibitor. Angioedema involving the tongue, glottis and/or larynx can be fatal. Emergency therapy should be initiated, including, but not necessarily limited to immediate subcutaneous injection of 0.3-0.5mg epinephrine or slow intravenous administration of 0.1mg epinephrine (dilution instructions to be observed) with ECG and blood pressure monitoring. Patients have to be hospitalised. Suitable monitoring should be initiated over a minimum of 12 to 24 hours in order to ensure complete resolution of the symptoms before the patient is discharged from hospital.

ACE-inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Aortic stenosis / Hypertrophic cardiomyopathy
ACE-inhibitors should be used with caution in patients with left ventricular outflow tract obstructions. If the obstruction is haemodynamically relevant, lisinopril is contra-indicated.

Neutropenia / Agranulocytosis
The risk of neutropenia appears to be dose-and-type related and is dependent on patient's clinical status. Neutropenia and agranulocytosis rarely have been observed in hypertensive patients treated with ACE-inhibitors. It is rarely seen in patients with uncomplicated hypertension but where more common in patients with renal impairment especially if associated with collagen vascular disease (e.g. systemic lupus erythematosus or scleroderma) or concurrent treatment with immunosuppressive agents. Regular white cell counts should be obtained in those patients. Neutropenia and agranulocytosis are reversible after withdrawal of the ACE-inhibitor.

Cough
Cough has been reported with the use of ACE-inhibitors. It is characteristically non-productive, persistent and resolves after discontinuation of therapy.

Surgery / Anaesthesia
Lisinopril blocks angiotensin II formation secondary to compensatory renin release in patients undergoing major surgery or anaesthesia with agents that produce hypotension. Resultant hypotension can be corrected by volume expansion (*see section 4.5*).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
When a diuretic is administered concomitantly with lisinopril treatment, the antihypertensive effect is generally additive.

Patients already in treatment with diuretics and especially those patients, whom the diuretic has been instituted recently, may occasionally experience a fall in blood pressure when lisinopril is added to the therapy. The risk of symptomatic hypotension during treatment with lisinopril can be reduced by discontinuing the diuretic prior to starting ByZestra. (*see section 4.4* and *section 4.2*).

Potassium-sparing diuretics or potassium supplements
Additive potassium-enhancing the effects can occur with potassium-sparing diuretics, particularly in patients with renal impairment.

ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements or potassium containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of documented hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Sodium chloride
Reduces the blood pressure lowering and heart failure symptom improving effect of lisinopril.

Antihypertensive agents
Increase the blood pressure lowering and heart failure symptom improving effect of lisinopril.

Analgesic and anti-inflammatory agents
(e.g acetylsalicylic acid, indomethacin): may reduce the blood pressure lowering effect of lisinopril.

Lithium
As with therapy involving other drugs that promote sodium excretion, lithium clearance may be lowered. Serum lithium levels should therefore be monitored carefully if lithium salts are to be administered. The posology should be adapted when necessary.

Alcohol
ACE inhibitors increase the effect of alcohol. Alcohol enhances the hypotensive effects of ACE inhibitors.

Anaesthetics/narcotics/hypnotics
Greater blood pressure fall (so the anaesthetist has to be informed of lisinopril therapy).

Sympathomimetics
May reduce the antihypertensive effects of ACE inhibitors.
An increased risk of leucopenia has been noted with the concomitant administration of allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procaiamide.

Oral antidiabetics (e.g sulphonyl urea drugs/biguanides), insulin
ACE inhibitors may enhance the hypoglycaemic effects of antidiabetic medication, particularly during the first weeks of combined treatment.

Antacids
May reduce the bioavailability of ACE inhibitors.

Non- steroidal anti-inflammatory drugs
The administration of a non–steroidal anti-inflammatory agent may reduce the antihypertensive effect of lisinopril. Lisinopril exerts an additive effect on the increase of serum potassium , whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with comprised renal function.

4.6 Pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4)

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). (See section 5.3) Should exposure to ACE inhibitors 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 sections 4.3 and 4.4).

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
When driving vehicles or operating machines it should be taken in to account that occasional dizziness or weariness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed in association with lisinopril therapy or with other ACE inhibitors:

Cardiovascular system:
Occasionally, severe hypotension may occur after initiation of therapy or with increase of the dosage of lisinopril and/or diuretics. This occurs especially in certain risk groups, e.g. in patients suffering from salt or fluid deficiency after diuretic therapy, heart failure and severe or renal hypertension. Symptoms like dizziness, feeling of weakness, impaired vision, rarely accompanied by loss of consciousness (syncope), can occur.
Individual cases of tachycardia, palpitations, arrhythmia, chest pain, angina pectoris, myocardial infarction, transient ischemic attacks and stroke have been reported for ACE inhibitors in association with pronounced blood pressure fall.

If lisinopril is administered in acute myocardial infarction patients, occasionally- especially within the first 24 hours- second or third degree AV block and/or severe hypotension and/or renal impairment, in rare cases cardiogenic shock may occur.

Kidneys
Renal insufficiency may occur or be intensified. Acute renal failure has been reported in single cases.
Proteinuria, partly with simultaneous deterioration of renal function, has been observed.

Respiratory system
Occasionally, dry cough, sore throat, hoarseness and bronchitis, rarely dyspnoea, sinusitis, rhinitis, bronchospasm/asthma, pulmonal infiltration, stomatitis, glossitis and dry mouth may occur. In individual cases angioneurotic oedema involving the upper airways has caused foetal airway obstruction (*see section 4.4, Special warnings and precautions for use).*
Isolated cases of allergic alveolitis (eosinophilic pneumonia) have been described in relation to therapy with lisinopril.

Gastrointestinal tract/liver
Occasionally nausea, abdominal pain and indigestion, rarely vomiting, diarrhoea, constipation and loss of appetite can occur.

ACE inhibitors have rarely been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis and death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice the ACE inhibitor should be stopped and the patient should be monitored medically. In patients receiving ACE inhibitors individual cases of hepatic dysfunction, hepatitis, liver insufficiency, pancreatitis and ileus have been described In relation to therapy with ACE inhibitors.

Skin, vessels
Occasionally allergic skin reactions like rash can occur, rarely psoriasis, urticaria as well as angioneurotic oedema of the face, lips and/or limbs.
In isolated cases severe skin reactions like pemphigus, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been described. Skin reactions can be accompanied by fever, myalgia, arthralgia, vasculitis, eosinophilia, leucocytosis and/or increased ANA-tires.

In case of suspected serious skin reaction the attending physician has to be consulted immediately and therapy with lisinopril needs to be terminated.
Individual cases of psoriasis-like skin changes, photosensitivity, flush, diaphoresis, alopecia, onycholysis and exacerbation of Raynaud's disease have been observed with ACE inhibitor therapy.

Nervous system
Occasionally headache and tiredness, rarely somnolence, depressions, sleep disorders, impotence, peripheral neuropathy with parathesia, disorders of balance, muscle cramps, nervousness, confusion, tinnitus, blurred vision, taste disturbances and temporary loss of taste.

Laboratory parameters (blood, urine)
Occasionally haemoglobin, haematocrit, white cell count or platelets may be decreased. There have been rare reports of anaemia, thrombocytopenia, neutropenia oreosinophilia, and isolated reports of agranulocytosis or pancytopenia, especially in patients with impaired renal function, collagen disease or concurrent treatment with allopurinol, procainamide or certain immunosuppressive drugs.
In patients with a congenital deficiency concerning G-6-PDH individual cases of haemolytic anaemia have been reported.
Increases in serum creatinine, urea and potassium respectively decrease in serum sodium concentration may rarely occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. In patients with diabetes mellitus hyperkalemia have been observed.
Proteinuria may be increased in special cases *(see section 4.4*)
Elevation of liver enzymes and serum bilirubin has been reported in isolated cases.

Special remarks
The above mentioned laboratory parameters should be performed before and regularly during treatment with lisinopril.

Especially in the initial phase of treatment and in high-risk patients (patients with renal insufficiency, in collagen disease) as well as concurrent treatment with immunosuppressive or cytostatic agents, allopurinol and procainamide, serum electrolyte and serum creatinine concentrations as well as full blood count should be monitored.
Patients experiencing such symptoms as fever, lymph node swelling and/or sore throat in the course of lisinopril therapy should have a white cell count without delay.

4.9 Overdose

No case of overdose has been reported.
The most likely overdosage phenomenon would be severe hypotension, shock, bradycardia, electrolyte disturbances and renal failure, the normal treatment being an infusion with a standard saline solution.
Lisinopril can be eliminated from the blood by haemodialysis.

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Precautions should be taken against absorption such as gastric lavage, administration of absorbents or sodium sulphate should be instituted within 30 minutes of intake. Measures to hasten elimination may also be taken. If hypotension occurs, the patient should be placed in shock position and intravenously salt and volume supplementation should be given rapidly. Treatment with angiotension II should be considered. Bradycardia should be treated by administering atropine.

The use of pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors,
ATC code: C 09 AA 03

Lisinopril is an angiotensin converting enzyme inhibitor. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreases aldosterone secretion.
ACE is identical with kininase II. Thus lisinopril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angitensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension.

5.2 Pharmacokinetic properties

The bioavailability of lisinopril is about 29% with an inter-patient variation of 6-60%. Maximum plasma concentrations are reached within approximately 7 hours after oral administration. Food does not affect the rate or extent of absorption.

Lisinopril is not metabolised and the absorbed fraction is excreted completely unchanged in the urine. Following multiple dosing, lisinopril displayed an effective half-life of 12.6 hours. Most of the drug is eliminated during the earlier phase, which does not contribute to drug accumulation. The terminal phase probably represents a saturable binding to ACE and is not proportional to the dose. Lisinopril does not appear to bind to other plasma proteins than ACE.

Acute myocardial infarction patients tend to have a slightly longer time to peak concentrations. Impaired renal function reduces the excretion of lisinopril through the kidneys. Elderly patients have higher AUC values than younger patients. Dosage adjustment is recommended in patients with creatine clearance <70ml/min and in elderly (*see section 4.2, Posology and method of administration*). Lisinopril can be removed by dialysis.

5.3 Preclinical safety data

Lisinopril dihydrate is safe with regard to genotoxicity. 2-years carcinogenicity studies in rats and mice failed to show any evidence of carcinogenic effects

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate anhydrous
Magnesium stearate
Pregelatinised starch
Mannitol
Maize starch

6.2 Incompatibilities

Not Applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/aluminium foil blisters in cartons each containing 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ergha Healthcare Ltd.,
Damastown,
Mulhuddart,
Dublin 15

8 MARKETING AUTHORISATION NUMBER

PA 966/7/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 22 April 2005
Date of last renewal: 22 April 2010

10 DATE OF REVISION OF THE TEXT

September 2010