Zestril 5 mg, 10 mg and 20 mg

lisinopril dihydrate
Tablets

Composition

Each tablet contains lisinopril dihydrate equivalent to 5 mg, 10 mg or 20 mg of anhydrous lisinopril.

Pharmaceutical form

5 mg tablet: round, pink, uncoated, biconvex tablet.
10 mg tablet: round, pink, uncoated, biconvex tablet.
20 mg tablet: round, brownish-red, uncoated, biconvex tablet.
All tablets are marked on one side with a number denoting the tablet strength.

Therapeutic indications

Hypertension
Zestril is indicated in the treatment of hypertension and in renovascular hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents.

Congestive Heart Failure
Zestril is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digitalis (see Posology and method of administration).

Acute myocardial infarction
Zestril is indicated for the treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blocker.

Renal complications of diabetes mellitus
In normotensive insulin-dependent and hypertensive non-insulin dependent diabetes mellitus patients who have incipient nephropathy characterised by microalbuminuria, Zestril reduces urinary albumin excretion rate.

Posology and method of administration

Zestril should be administered orally in a single daily dose. As with all other medication taken once daily, Zestril should be taken at approximately the same time each day. The absorption of Zestril tablets is not affected by food.

The dose should be individualised according to patient profile and blood pressure response (see Special warnings and precautions for use).

Hypertension

Zestril may be used as monotherapy or in combination with other classes of antihypertensive therapy.

Starting dose
In patients with hypertension the usual recommended starting dose is 10 mg. 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 blood pressure fall following the initial dose. A starting dose of 2.5 - 5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose
The usual effective maintenance dosage is 20 mg administered in a single daily dose. In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can be further increased. The maximum dose used in long-term, controlled clinical trials was 80 mg/day.

Diuretic-treated patients
Symptomatic hypotension may occur following initiation of therapy with Zestril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, 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 Zestril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Zestril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Zestril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see Special warnings and precautions for use & Interactions).

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)	Starting Dose (mg/day)
less than 10 ml/min (including patients on dialysis)	2.5 mg*
10 - 30 ml/min	2.5 - 5 mg
31 - 80 ml/min	5 - 10 mg

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Use in Hypertensive Paediatric Patients aged 6-16 years
The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses

above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients (see Pharmacodynamics).

Zestril is not recommended in pediatric patients <6 years or in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2.

Congestive Heart failure
In patients with symptomatic heart failure, Zestril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Zestril may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Zestril should be increased:

- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks

The usual effective dosage range is 5 to 20 mg per day administered in a single daily dose.

Dose adjustment should be based on the clinical response of individual patients. 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 Zestril. Renal function and serum potassium should be monitored (see Special warnings and precautions for use).

Acute myocardial infarction
Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Zestril.

Starting dose (first 3 days after infarction)
Treatment with Zestril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mmHg. The first dose of Zestril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mmHg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see Special warnings & precautions for use).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose
The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour) Zestril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Zestril (see Posology and method of administration).

Renal complications of diabetes mellitus
In normotensive insulin-dependent diabetes mellitus patients, the daily dose is 10 mg Zestril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 75 mmHg. In hypertensive non-insulin-dependent diabetes mellitus patients, the dose schedule is as above to achieve a sitting diastolic blood pressure below 90 mmHg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Pediatric Use
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Zestril is not recommended in children in other indications than hypertension.

Use in the elderly
In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 should be used to determine the starting dose of Zestril. Thereafter, the dosage should be adjusted according to the blood pressure response.

Use in kidney transplant patients
There is no experience regarding the administration of Zestril in patients with recent kidney transplantation. Treatment with Zestril is therefore not recommended.

Contraindications

- Hypersensitivity to Zestril, to any of the excipients or any other angiotensin-converting enzyme (ACE) inhibitor.
- History of anaphylactic/anaphylactoid reactions or angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second or third trimesters of pregnancy (see Pregnancy and lactation).
- The concomitant use of Zestril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73m^2) (see Interaction with other medicinal products and other forms of interaction).

Special warnings and precautions for use

Symptomatic hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Zestril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see Interactions and Undesirable effects). In patients with congestive 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. 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 Zestril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Zestril may be necessary.

Hypotension in acute myocardial infarction
Treatment with Zestril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then Zestril should be withdrawn.

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 the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Contraindications and Interactions).

If dual blockade therapy is considered 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.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, Zestril 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 function impairment
In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in Posology and method of administration) and then as a function of the patient's response

to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with congestive 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 Zestril 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 Zestril 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 Zestril may be required.

In acute myocardial infarction, treatment with Zestril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with Zestril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of Zestril.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with angiotensin converting enzyme inhibitors, including Zestril. This may occur at any time during therapy. In such cases, Zestril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases 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.

ACE 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).

Some drugs if given concomitantly with ACE inhibitors may increase the risk of angioedema (see Interactions)

Anaphylactoid reactions in haemodialysis patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) 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.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis
Rarely, patients receiving ACE inhibitors during low-density lipoproteins (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.

Desensitisation
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

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

Neutropenia/Agranulocytosis
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. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Zestril 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 Zestril 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, Zestril may be less effective in lowering blood pressure in black patients 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.

Antihypertensive agents
When combined with other antihypertensive agents, additive falls in blood pressure may occur.

Concomitant use of aliskiren-containing medicines with angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors should be avoided (see Contraindications and Special warnings and precautions for use).

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. 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 Zestril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, 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 (see Interactions).

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 Interactions).

Lithium
The combination of lithium and Zestril is generally not recommended (see Interactions).

Pregnancy and lactation

Lisinopril should not be used during the first trimester of pregnancy. Zestril is contraindicated in the second and third trimesters of pregnancy (see Contraindications). When pregnancy is detected, lisinopril treatment should discontinue as soon as possible (see Pregnancy and lactation).

Use of lisinopril is not recommended during breast-feeding.

Interactions

Diuretics
When a diuretic is added to the therapy of a patient receiving Zestril the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when Zestril is added. The possibility of symptomatic hypotension with Zestril can be minimised by discontinuing the diuretic prior to initiation of treatment with Zestril (see Special warnings and precautions for use and Posology and method of administration).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels
Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes and other drugs that may increase serum potassium levels (e.g., heparin, co-trimoxazole).

The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If Zestril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

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 lithium toxicity with ACE inhibitors. Use of Zestril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see Special warnings and precautions for use).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥3 g/day
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and many 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 the elderly or dehydrated.

Gold
Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Antihypertensive agents

When combined with other antihypertensive agents, additive falls in blood pressure may occur. Clinical trial data has shown that dual blockade of the 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 and Special warnings and precautions for use).

Concomitant use of these agents may increase the hypotensive effects of Zestril. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Drugs that may increase the risk of angioedema
Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) or tissue plasminogen activator may increase the risk of angioedema.

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 Special warnings and precautions for use).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
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
Zestril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

Pregnancy and lactation

Pregnancy
Zestril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated 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.

Zestril is contraindicated during the second and third trimester 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 Zestril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken Zestril should be closely observed for hypotension, oliguria and hyperkalaemia. Zestril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation
It is not known whether Zestril is secreted in human breast milk. Lisinopril is excreted into the milk of lactating rats. The use of Zestril is not recommended in women who are breast-feeding.

Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

Undesirable effects

The following undesirable effects have been observed and reported during treatment with Zestril and other ACE inhibitors with the following frequencies: Very common (≥10%), common (≥1%, <10%), uncommon (≥0.1, <1%), rare (≥0.01, <0.1%), very rare (<0.01%) including isolated reports.

Blood and the lymphatic system disorders:

rare:	decreases in haemoglobin, decreases in haematocrit
very rare:	bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see Special warnings and precautions for use), haemolytic anaemia, lymphadenopathy, autoimmune disease.

Immune system disorders:

not known:	anaphylactic/anaphylactoid reaction

Metabolism and nutrition disorders:

very rare:	hypoglycaemia

Nervous system and psychiatric disorders:

common:	dizziness, headache
uncommon:	mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances, hallucinations
rare:	mental confusion, olfactory disturbance
not known:	depressive symptoms, syncope

Cardiac and vascular disorders:

common:	orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see Special warnings and precautions for use), palpitations, tachycardia. Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:
common: cough
uncommon: rhinitis
very rare: bronchospasm, sinusitis. Allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
common: diarrhoea, vomiting
uncommon: nausea, abdominal pain and indigestion
rare: dry mouth
very rare: pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see Special warnings and precautions for use)

Skin and subcutaneous tissue disorders:
uncommon: rash, pruritus, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see Special warnings and precautions for use)
rare: urticaria, alopecia, psoriasis
very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:
common: renal dysfunction
rare: uraemia, acute renal failure
very rare: oliguria/anuria

Endocrine disorders:
not known: inappropriate antidiuretic hormone secretion

Reproductive system and breast disorders:
uncommon: impotence
rare: gynaecomastia

General disorders and administration site conditions:
uncommon: fatigue, asthenia

Investigations:
uncommon: increases in blood urea, increases in serum creatinine, increases in

liver enzymes, hyperkalaemia
rare: increases in serum bilirubin, hyponatraemia

Safety data from clinical studies suggest that lisinopril is generally well tolerated in hypertensive paediatric patients, and that the safety profile in this age group is comparable to that seen in adults.

Overdose

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

The recommended treatment of overdose 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 and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Zestril (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Zestril may be removed from the general circulation by haemodialysis (see Special warning and precautions for use). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors
ATC code: C09AA03.

Zestril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of Zestril and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394, patients who were administered the treatment within 24 hours of an acute myocardial infarction, Zestril produced a statistically significant risk reduction in mortality of 11% versus control (2p=0.03). The risk reduction with glyceryl trinitrate was not significant but the combination of Zestril and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control (2p=0.02). In the sub-groups of elderly (age >70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was

observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with Zestril or Zestril plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for Zestril. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with Zestril treatment but these were not associated with a proportional increase in mortality.

In a double-blind, randomised, multicentre trial which compared Zestril with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, Zestril 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with Zestril showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of Zestril reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.

ACE is known to be present in the endothelium and increased ACE activity in diabetic patients which results in the formation of angiotensin II and destruction of bradykinin, potentiates the damage to the endothelium caused by hyperglycaemia. ACE inhibitors, including lisinopril, inhibit the formation of angiotensin II and breakdown of bradykinin and hence ameliorate endothelial dysfunction.

Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA1c).

In a clinical study involving 115 paediatric patients with hypertension, aged 6-16 years, patients who weighed less than 50 kg received either 0.625 mg, 2.5 mg or 20 mg of Zestril once a day, and patients who weighed 50 kg or more received either 1.25 mg, 5 mg or 40 mg of Zestril once a day. At the end of 2 weeks, Zestril administered once daily lowered trough blood pressure in a dose-dependent manner with a consistent antihypertensive efficacy demonstrated at doses greater than 1.25 mg.
This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mm Hg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of Zestril. The dose-dependent antihypertensive effect of Zestril was consistent across several demographic subgroups: age, Tanner stage, gender, and race.

Pharmacokinetic properties

Lisinopril is an orally active non-sulphydryl-containing ACE inhibitor.

Absorption
Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced to

approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Distribution
Lisinopril does not appear to be bound to serum proteins other than to circulating angiotensin converting enzyme (ACE). Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination
Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50ml/min. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment
Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%) compared to healthy subjects due to decreased clearance.

Renal impairment
Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30ml/min).

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55ml/min.

Heart failure
Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

Elderly
Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects.

Paediatrics
The pharmacokinetic profile of lisinopril was studied in 29 paediatric hypertensive patients, aged between 6 and 16 years, with a GFR above 30 ml/min/1.73 m^2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours, and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults.

AUC and C_{max} values in children in this study were consistent with those observed in adults.

List of excipients
Mannitol Ph. Eur.
Calcium hydrogen phosphate dihydrate Ph. Eur.
Red iron oxide (E172)
Maize starch Ph. Eur.
Pregelatinised starch Ph. Eur.
Magnesium stearate Ph. Eur.

Shelf-life
Please refer to expiry date on the blister strip or outer carton.

Special precautions for storage
Do not store above 30ºC

Pack size
Please refer to the outer carton for pack size.

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