

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.

For the full list of excipients, see List of excipients.

Pharmaceutical form

5 mg tablets: round, pink, uncoated, biconvex tablet with "5" on one side and bisected on the other side. Diameter 6 mm. The tablet can be divided into equal doses.

10 mg tablets: round, pink, uncoated, biconvex tablet with "10" on one side and plain on the other side. Diameter 8 mm.

20 mg tablets: round, brownish-red, uncoated, biconvex tablet with "20" on one side and plain on the other side. Diameter 8 mm.

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.

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-blockers.

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 (see Contraindications, Special warnings and precautions for use, Interactions and Pharmacodynamic properties).

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 and 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.

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
- To the highest dose tolerated by the patient up to a maximum of 35 mg once daily

High doses reduce the risk of the combined outcomes of mortality and hospitalization.

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 and 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).

Paediatric use

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

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 listed in List of excipients or any other angiotensin-converting enzyme (ACE) inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see Special warnings and precautions for use and Fertility, 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/1.73m²) (see Interactions and Pharmacodynamic properties).

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

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		CMO Code	AIP538047A			
MY	Pharmanovia Code	704-4381	Previous Ref.	CN62-902		
Date	06-02-23	Version	06	Size	170x315mm	
Description	ZESTRIL 5MG 10MG 20MG TABLETS 28		Tech. Drawing	ZG ROVI APIL 170x315 mm L2		
Pharmanovia Previous Code	703-7625		128 Code	553804701		
			Edge Marks	N/A		
			Min. Font Size	7 pt	Min. Code Size	6 pt
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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 those in 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.

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 with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin-converting enzyme 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 rarely 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.

Angiotensin-converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see Contraindications).

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Interactions and Pharmacodynamic properties).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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.

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 (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, the combination trimethoprim/sulfamethoxazole also known as co-trimoxazole). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see Interactions).

Lithium

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

Pregnancy

There is an increased risk of birth defects, foetal and neonatal morbidity and death when used throughout pregnancy. ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see Contraindications and Fertility, pregnancy and lactation).

Interactions

Antihypertensive agents






When Zestril is combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting

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<p>agent (see sections Contraindications, Special warnings and precautions for use and Pharmacodynamic properties).</p> <p>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 plasminogenactivator may increase the risk of angioedema.</p> <p>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 <i>Special warnings and precautions for use and Posology and method of administration</i>).</p> <p>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. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. Monitoring of potassium should be undertaken as appropriate (see <i>Special warnings and precautions for use</i>). If Zestril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.</p> <p>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 <i>Special warnings and precautions for use</i>).</p> <p>Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥3 g/day When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. These effects are usually reversible. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.</p> <p>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.</p> <p>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 <i>Special warnings and precautions for use</i>).</p> <p>Sympathomimetics Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.</p> <p>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.</p> <p>Co-trimoxazole (trimethoprim/sulfamethoxazole) Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see <i>Special warnings and precautions for use</i>).</p> <p>Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates Zestril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.</p> <p>Fertility, pregnancy and lactation</p> <p>Pregnancy There is an increased risk of birth defects, foetal and neonatal morbidity and death when used throughout pregnancy. The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see <i>Special warnings and precautions for use</i>). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see <i>Contraindications and Special warnings and precautions for use</i>).</p> <p>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 inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.</p> <p>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 <i>Preclinical safety data</i>).</p> <p>Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and the</p>	<p>skull is recommended.</p> <p>Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see <i>Contraindications and Special warnings and precautions for use</i>).</p> <p>Breastfeeding Because no information is available regarding the use of Zestril during breastfeeding, Zestril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.</p> <p>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.</p> <p>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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).</p> <p>Blood and the lymphatic system disorders</p> <p>rare: decreases in haemoglobin, decreases in haematocrit</p> <p>very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see <i>Special warnings and precautions for use</i>), haemolytic anaemia, lymphadenopathy, autoimmune disease.</p> <p>Immune system disorders</p> <p>not known: anaphylactic/anaphylactoid reaction.</p> <p>Metabolism and nutrition disorders</p> <p>very rare: hypoglycaemia.</p> <p>Nervous system and psychiatric disorders</p> <p>common: dizziness, headache</p> <p>uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances, hallucinations</p> <p>rare: mental confusion, olfactory disturbance</p> <p>frequency not known: depressive symptoms, syncope.</p> <p>Cardiac and vascular disorders</p> <p>common: orthostatic effects (including hypotension) myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see <i>Special warnings and precautions for use</i>), palpitations, tachycardia. Raynaud's phenomenon.</p> <p>uncommon: phenomenon.</p> <p>Respiratory, thoracic and mediastinal disorders</p> <p>common: cough</p> <p>uncommon: rhinitis</p> <p>very rare: bronchospasm, sinusitis. Allergic alveolitis/eosinophilic pneumonia.</p> <p>Gastrointestinal disorders</p> <p>common: diarrhoea, vomiting</p> <p>uncommon: nausea, abdominal pain and indigestion</p> <p>rare: dry mouth</p> <p>very rare: pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see <i>Special warnings and precautions for use</i>).</p> <p>Skin and subcutaneous tissue disorders</p> <p>uncommon: rash, pruritus</p> <p>rare: urticaria, alopecia, psoriasis, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see <i>Special warnings and precautions for use</i>)</p> <p>very rare: sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.</p> <p>A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.</p> <p>Renal and urinary disorders</p> <p>common: renal dysfunction</p> <p>rare: uraemia, acute renal failure</p> <p>very rare: oliguria/anuria.</p> <p>Endocrine disorders</p> <p>rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH).</p> <p>Reproductive system and breast disorders</p> <p>uncommon: impotence</p> <p>rare: gynaecomastia.</p> <p>General disorders and administration site conditions</p> <p>uncommon: fatigue, asthenia.</p> <p>Investigations</p> <p>uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia</p> <p>rare: increases in serum bilirubin, hyponatraemia.</p> <p>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.</p>
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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: C09A A03.

Mechanism of Action
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.

Pharmacodynamic effects
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.

Clinical efficacy and safety
The effect of Zestril on mortality and morbidity in congestive heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164 patients, with a median follow up period of 46 months for surviving patients, high dose Zestril produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation (p = 0.002) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation (p = 0.036) compared with low dose. Risk reductions for all-cause mortality (8%; p = 0.128) and cardiovascular mortality (10%; p = 0.073) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p = 0.002) in patients treated with high-dose Zestril compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of Zestril. The results of the study showed that the overall adverse event profiles for patients treated with high or low dose Zestril were similar in both nature and number. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose Zestril compared with low dose.

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.

Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycosylated haemoglobin (HbA_{1c}). Renin-angiotensin system (RAS)-acting agents
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end organ damage. VA NEPHRON D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers. ACE inhibitors and angiotensin II receptor blockers should therefore

not be used concomitantly in patients with diabetic nephropathy. ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

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 circulation 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 50 ml/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 5-30 ml/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 55 ml/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
Elderly have higher blood levels and higher values for the area under the plasma concentration-time curve (increased approximately 60%) compared with younger subjects.

Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin-converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

List of excipients
Mannitol
Calcium hydrogen phosphate dihydrate
Red iron oxide
Maize starch
Pregelatinised starch
Magnesium stearate

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

Special precautions for storage
Do not store above 30°C

Nature and contents of container
Aluminium/PVC-PVDC or Aluminium/PVC foil blister calendar packs of 28 tablets.

Manufacturer
ROVI Pharma Industrial Services S. A.,
Via Complutense, 140,
Alcalá de Henares, Madrid, 28805
Spain

Date of revision of text
January 2023



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FREE TEXT AREA

RESERVED AREA CODE



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		Manufacturer	ROVI														
		CMO Code	AIP538047A														
<table border="1"> <tr> <td>MY</td> <td>Pharmanovia Code</td> <td>704-4381</td> </tr> <tr> <td>Date</td> <td>06-02-23</td> <td>Version 06</td> </tr> <tr> <td>Description</td> <td colspan="2">ZESTRIL 5MG 10MG 20MG TABLETS 28</td> </tr> <tr> <td>Pharmanovia Previous Code</td> <td colspan="2">703-7625</td> </tr> </table>		MY	Pharmanovia Code	704-4381	Date	06-02-23	Version 06	Description	ZESTRIL 5MG 10MG 20MG TABLETS 28		Pharmanovia Previous Code	703-7625		Previous Ref.	CN62-902		
		MY	Pharmanovia Code	704-4381													
Date	06-02-23	Version 06															
Description	ZESTRIL 5MG 10MG 20MG TABLETS 28																
Pharmanovia Previous Code	703-7625																
		Size	170x315mm														
		Tech. Drawing	ZG ROVI APIL 170x315 mm L2														
		128 Code	553804701														
		Edge Marks	N/A														
		Min. Font Size	7 pt	Min. Code Size	6 pt												
		Notes															
		Printable Colours	 Black														
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		Non Printable Colours	