ZESTORETIC

Lisinopril dihydrate hydrochlorothiazide

Tablets

Composition

Each tablet contains lisinopril dihydrate (equivalent to 20 mg anhydrous lisinopril) and 12.5 mg hydrochlorothiazide Ph Eur.

Pharmaceutical form

White, round, biconvex, uncoated tablets.

Therapeutic indication

Zestoretic is indicated in the treatment of essential hypertension for patients in whom combination therapy is appropriate.

Posology and method of administration

Essential hypertension

The usual dosage is one tablet, administered once daily. As with all other medication taken once daily, Zestoretic should be taken at approximately the same time each day.

In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

Dosage in renal insufficiency

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).

Zestoretic is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, Zestoretic may be used, but only after titration of the individual components.

The recommended initial dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10 mg.

Prior diuretic therapy

Symptomatic hypotension may occur following the initial dose of Zestoretic; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Zestoretic. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Paediatric use

Safety and effectiveness in children have not been established.

Use in the elderly

In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Lisinopril, within a daily dosage range of 20 to 80 mg, was equally effective in elderly (65 years or older) and non-elderly hypertensive patients. In elderly hypertensive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

Contraindications

Zestoretic is contraindicated in patients with anuria.

Zestoretic is contraindicated in patients who are hypersensitive to any component of this product, in patients with a history of angioedema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

Zestoretic is contraindicated in patients who are hypersensitive to other sulphonamide-derived drugs.

Zestoretic is contraindicated in second and third trimesters of pregnancy (see "Pregnancy and lactation").

Special warnings and precautions for use

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients but is more likely in the presence of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur from prior diuretic therapy, dietary salt restriction, dialysis, or during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision.

Particular consideration should be given when therapy is administered to patients with ischaemic heart or cerebrovascular disease because 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. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

As with other vasodilators, Zestoretic should be given with caution to patients with aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).

Zestoretic should not be administered to patients with renal insufficiency (creatinine clearance less than or equal to 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

In some patients with bilateral renal artery stenosis or 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, renal function should be monitored during the first few weeks of Zestoretic therapy.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy with Zestoretic, the combination should be discontinued. Reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

Hepatic disease

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril 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.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

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 Zestoretic. This may occur at any time during therapy. In such cases, Zestoretic should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with anti-histamines 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 also "Contraindications").

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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 reappeared upon inadvertent rechallenge.

Haemodialysis patients

The use of Zestoretic is not indicated in patients requiring dialysis for renal failure.

Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

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.

Interactions

Potassium supplements, potassium-sparing agents or potassium-containing salt substitutes

The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of Zestoretic and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Lithium generally should not be given with diuretics or ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the prescribing information for lithium preparations before use of such preparations.

Antihypertensive agents

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

Other agents

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered hydrochlorothiazide and lisinopril. In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs), the co-administration of lisinopril may result in a further deterioration in renal function.

Thiazides may increase the responsiveness to tubocurarine.

Pregnancy and lactation

Use in pregnancy

Zestoretic is contraindicated in the second and third trimesters of pregnancy (see "Contraindications"). The use of Zestoretic is not recommended during the first trimester of pregnancy. When pregnancy is detected, lisinopril should be discontinued as soon as possible.

ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. Use of ACE inhibitors during the period has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalaemia and/or skull hypoplasia in the new-born. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE inhibitor exposure limited to the first trimester.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

If lisinopril is used during the first trimester of pregnancy, the patient should be informed of the potential hazard to the foetus. Should exposure to Zestoretic have occurred during the second or third trimesters of pregnancy, serial ultrasound examinations should be performed to assess the intra-amniotic environment. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

Infants whose mothers may have taken lisinopril should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril, 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. There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

Lactation

It is not known whether lisinopril is secreted in human milk; however, thiazides do appear in human milk. Because of the potential for serious reactions from hydrochlorothiazide in breast-fed infants, a decision should be made whether to discontinue breast feeding or to discontinue Zestoretic, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines

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

Undesirable effects

Clinical trials

Zestoretic is usually well tolerated. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy. The side effects that have been observed have been limited to those reported previously with lisinopril or hydrochlorothiazide.

One of the most common clinical side effects was dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy.

Other side effects were headache, cough, fatigue and hypotension including orthostatic hypotension.

Post marketing

The following undesirable effects have been observed and reported during treatment with Zestoretic 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: anaemia.
Very rare: bone marrow depression, thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia.

Metabolism and nutrition disorders
Uncommon: gout.
Rare: hyperglycaemia, hypokalaemia, hyperuricemia, hyperkalaemia.

Nervous system and psychiatric disorders:
Common: dizziness, headache, paraesthesia.

Cardiac and vascular disorders:
Common: orthostatic effects (including hypotension).
Uncommon: palpitations.

Respiratory, thoracic and mediastinal disorders:
Common: cough.

Gastrointestinal disorders:
Common: diarrhoea, nausea, vomiting.
Uncommon: dry mouth.
Rare: pancreatitis
Very rare: intestinal angioedema.

Hepato-biliary disorders
Very rare hepatitis- either hepatocellular or cholestatic, jaundice, hepatic failure. Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving Zestoretic who develop jaundice or marked elevation of hepatic enzymes should discontinue Zestoretic and receive appropriate medical follow up.

Skin and subcutaneous tissue disorders:
Common: rash.

Rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see "Special warnings and precautions for use")

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.

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

Reproductive system and breast disorders:
Common: impotence.

General disorders and administration site conditions:
Common: fatigue, asthenia.
Uncommon: chest discomfort

Investigations:
Common: increases in blood urea , increases in serum creatinine, increases in liver enzymes, decreases in haemoglobin.
Uncommon: decreases in haematocrit.
Rare: increases in serum bilirubin.

Other side effects reported with the individual components alone, and which may be potential side effects with Zestoretic, are:

Hydrochlorothiazide: anorexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance including hyponatraemia, muscle spasm, restlessness, transient blurred vision, renal failure, renal dysfunction and interstitial nephritis.

Lisinopril: myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients, tachycardia, abdominal pain and indigestion, mood alterations, mental confusion and vertigo have occurred; as with other angiotensin converting enzyme inhibitors, taste disturbance and sleep disturbance have been reported; bronchospasm, rhinitis, sinusitis, alopecia, urticaria, diaphoresis, pruritus, psoriasis and severe skin disorders, (including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme), have been reported; hyponatraemia, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, pancreatitis. Rarely, haemolytic anaemia has been reported.

Overdose

No specific information is available on the treatment of overdosage with Zestoretic. Treatment is symptomatic and supportive. Therapy with Zestoretic should be discontinued

and the patient should be kept under very close supervision. Therapeutic measures depend on the nature and severity of the symptoms. Measures to prevent absorption and methods to speed elimination should be employed.

Lisinopril: The most likely features of overdosage would be hypotension, electrolyte disturbance and renal failure. If severe hypotension occurs, the patient should be placed in the shock position and an intravenous infusion of normal saline should be given rapidly. Treatment with angiotensin II (if available) may be considered. Angiotensin converting enzyme inhibitors may be removed from the general circulation by haemodialysis. The use of high-flux polyacrylonitrile dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.

Hydrochlorothiazide: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

Pharmacodynamic properties

Zestoretic is a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complimentary modes of action and exert an additive antihypertensive effect.

Lisinopril 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.

While 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.

Hydrochlorothiazide is a diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Pharmacokinetic properties

Concomitant administration of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

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 of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced 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 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.

Table 1. Pharmacokinetic parameters of lisinopril to different groups of renal patients after administration of a multiple 5 mg dose

Renal Function Measured by creatinine clearance	n	Cmax (ng/ml)	Tmax (hr)	AUC (0-24 hrs) (ng/hr/ml)	$t_{1/2}$ (hr)
> 80 ml/min	6	40.3	6	492+/-172	6.0+/-1.1
30-80 ml/min	6	36.6	8	555+/-364	11.8+/-1.9
5-30 ml/min	6	106.7	8	2228+/-938	19.5+/-5.2

With a creatinine clearance of 30-80ml/min, mean AUC was increased by 13% only, while a 4-5 fold increase in mean AUC was observed with creatinine clearance of 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 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
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

Hydrochlorothiazide: When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

List of excipients
Mannitol
Calcium Hydrogen Phosphate
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. Protect from light.

Pack size
Please refer to outer carton for pack size.

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