PRODUCT MONOGRAPH

Pr Mylan-Lisinopril HCTZ

Lisinopril and Hydrochlorothiazide Tablets

10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg

Pharmaceutical standard: Mfr. Std

Angiotensin Converting Enzyme Inhibitor/Diuretic

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Date of Revision:
December 01, 2014

Submission Control number: 179824

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Lisinopril and Hydrochlorothiazide Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Nonmedicinal Ingredients
Oral	Tablets: 10 mg/12.5 mg, 20 mg/12.5 mg and 20 mg/25 mg	Dibasic calcium phosphate, magnesium stearate, mannitol, starch and talc. The 10 mg/12.5 mg and 20 mg/25 mg strengths also contain iron oxide yellow and iron oxide red.

INDICATIONS AND CLINICAL USE

Mylan-Lisinopril HCTZ (lisinopril and hydrochlorothiazide) is indicated for:

- The treatment of essential hypertension in patients for whom combination therapy is appropriate.

In using Mylan-Lisinopril HCTZ, consideration should be given to the risk of angioedema (see WARNINGS AND PRECAUTIONS, Immune).

Lisinopril should normally be used in those patients in whom treatment with diuretic or beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

Mylan-Lisinopril HCTZ is not indicated for initial therapy. Patients in whom lisinopril and diuretic are initiated simultaneously can develop symptomatic hypotension (see DRUG INTERACTIONS).

Patients should be titrated on the individual drugs. If the fixed combination represents the dosage determined by this titration, the use of Mylan-Lisinopril HCTZ may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use individual drugs.

Geriatrics (> 65 years of age): In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Pediatrics: Lisinopril and hydrochlorothiazide has not been studied in children and, therefore, use in this age group is not recommended.

CONTRAINDICATIONS

Mylan-Lisinopril HCTZ (lisinopril and hydrochlorothiazide) is contraindicated in:

- Patients who are hypersensitive to any component of this product;
- Patients with a known allergy to angiotensin converting enzyme inhibitors;
- Patients with a history of angioneurotic edema relating to previous treatment with an angiotensin converting enzyme inhibitor;
- Patients who have hereditary or idiopathic angioneurotic edema, and because of the hydrochlorothiazide component, in patients who have anuria;
- Patients who are hypersensitive to other sulfonamide-derived drugs.
- Patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) who are taking aliskiren-containing drugs. Concomitant use of angiotensin converting enzyme (ACE) inhibitors, including the lisinopril component of lisinopril and hydrochlorithiazide, with aliskiren-containing drugs in patients with diabetes mellitus or moderate to severe renal impairment is contraindicated (see WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, MYLAN-LISINOPRIL HCTZ should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women)

Cardiovascular

Dual blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as the lisinopril component in lisinopril and hydrochlorothiazide, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration

of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). Therefore, the use of Mylan-Lisinopril HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including the lisinopril component of lisinopril and hydrochlorothiazide, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Hypotension: Symptomatic hypotension has occurred after administration of lisinopril, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Therefore, Mylan-Lisinopril HCTZ should not be used to start therapy or when a dose change is needed. Severe hypotension is also a risk in renin-dependant renovascular hypertension; Mylan-Lisinopril HCTZ is not indicated for this condition (see INDICATIONS AND CLINICAL USE). In patients with ischemic heart or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because blood pressure could potentially fall, patients at risk for hypotension should start lisinopril therapy under very close medical supervision, usually in a hospital. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of lisinopril and/or hydrochlorothiazide is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response may not be a contraindication to further doses. These can usually be given to hypertensive patients without difficulty once the blood pressure has increased after volume expansion. Reinstitution of therapy at reduced dosages, or re-institution with either component alone, should be considered.

Valvular Stenosis, Hypertrophic Cardiomyopathy: There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much after load reduction.

Mylan-Lisinopril HCTZ should be given with caution to patients with aortic or hypertrophic cardiomyopathy.

Ear/Nose/Throat

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of lisinopril and hydrochlorothiazide, has been reported.

Such possibility should be considered as part of the differential diagnosis of the cough.

Endocrine and Metabolism

Metabolism: Thiazide therapy may impair glucose tolerance. Dosage adjustment of hypoglycemic agents may be required (see DRUG INTERACTIONS).

Hyperuricemia may occur, or acute gout may be precipitated, in certain patients receiving thiazide therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Hyperkalemia: In clinical trials hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 1.4% of hypertensive patients. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes (see **DRUG INTERACTIONS**).

Hematologic

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by angiotensin converting enzyme inhibitors. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function: Hepatitis (with very rare progression to hepatic failure), jaundice (hepatocellular and/or cholestatic), marked elevations of liver enzymes and/or serum bilirubin have occurred during therapy with lisinopril in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug, and appropriate medical follow up.

Should the patient receiving Mylan-Lisinopril HCTZ experience any unexplained symptoms, particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of Mylan-Lisinopril HCTZ should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Mylan-Lisinopril HCTZ should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

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.

Immune

Hypersensitivity Reactions: Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Angioedema: Angioedema has been uncommonly reported in patients treated with lisinopril and hydrochlorothiazide and may occur at any time during therapy. Angioedema associated with laryngeal or tongue edema and/or shock may be fatal. If angioedema occurs, Mylan-Lisinopril HCTZ should be promptly discontinued and the patient should be treated, and observed until the swelling subsides. Where swelling is confined only to the tongue, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, and especially in cases where there has been a history of airway surgery, emergency therapy should be administered promptly when indicated. This includes giving subcutaneous adrenaline/epinephrine (0.5 mL 1:1000) and/or maintaining a patent airway. The patient should be under close medical supervision until the complete and sustained symptom resolution has occurred.

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black 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).

Anaphylactoid Reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN] and during low density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor.

Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Anaphylactoid Reactions during desensitization:
There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Neurologic
Ability to Drive and Use Machines: Dizziness or tiredness may occur during treatment with lisinopril and hydrochlorothiazide.

Ophthalmologic

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue lisinopril and hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Peri-Operative Considerations

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril blocks 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. (see DRUG INTERACTIONS).

Renal

Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

The use of ACE inhibitors, including the lisinopril component of lisinopril and hydrochlorothiazide, or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60 ml/min/1.73m^2) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).

Use of Mylan-Lisinopril HCTZ (lisinopril and hydrochlorothiazide) should include appropriate assessment of renal function.

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 (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Azotemia: Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

Special Populations

Pregnant Women: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, Mylan-Lisinopril HCTZ should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

Infants with a history of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

Lisinopril, has been removed from the neonatal circulation by peritoneal dialysis.

Animal Data: Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1000 mg/kg, this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.

Fetotoxicity was demonstrated in rabbits by an increase incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death.

By whole body autoradiography, radioactivity was found in the placenta following administration of labelled lisinopril to pregnant rats, but none was found in the fetuses.

Nursing Women: The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

Pediatrics: Lisinopril and hydrochlorothiazide has not been studied in children and, therefore, use in this age group is not recommended.

Geriatrics (> 65 years of age): In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Race: Angiotensin converting inhibitors cause a higher rate of angioedema in black patients than in non black patients.

The antihypertensive effect of angiotensin converting enzyme inhibitors is generally lower in black patients (usually a low-renin hypertensive population) than in non-black patients.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials involving 930 patients, including 100 patients treated for 50 weeks or more, the most severe clinical adverse reactions were syncope (0.8%), and hypotension (1.9%). The most frequent clinical adverse reactions were: dizziness (7.5%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%).

Discontinuation of treatment due to adverse reactions occurred in 4.4% of patients, mainly because of dizziness, cough, fatigue or muscle cramps.

Adverse reactions that have occurred in clinical trials or in marketing experience are those which have been previously reported with lisinopril and hydrochlorothiazide when used separately for the treatment of hypertension.

Adverse reactions occurring in hypertensive patients treated with lisinopril and hydrochlorothiazide in controlled trials are shown in Table 1.

Table 1 Incidence of Adverse Reactions Occurring in Patients Treated with Lisinopril and hydrochlorothiazide In Controlled Clinical Trials

	Lisinopril Plus Hydrochlorothiazide n=930 (%)	Lisinopril n=2633 (%)
Body as a whole		
fatigue	3.7	-
asthenia	1.8	2.7
impotence	1.2	0.7
decreased libido	1.0	0.2
fever	0.5	0.3
gout	0.2	0.2
Cardiovascular		
orthostatic effects	3.2	0.9
hypotension	1.9	0.8
chest pain	1.0	1.1
palpitation	0.9	0.8
syncope	0.8	0.2
chest discomfort	0.6	-
edema	0.1	0.6
rhythm disturbances	0.1	0.5
angina	0.1	0.3
Digestive		
diarrhea	2.5	1.8
nausea	2.2	1.9
vomiting	1.4	1.1
dyspepsia	1.3	0.5
abdominal pain	0.9	1.4
constipation	0.3	0.2
dry mouth	0.2	0.5
anorexia	0.2	0.4
flatulence	0.2	0.3
Dermatologic		
rash	1.2	1.0
flushing	0.8	0.3
pruritis	0.4	0.5
angiodema	-*	0.1
Musculoskeletal		
Muscle cramps	2.0	0.5
Back pain	0.8	0.5
Shoulder pain	0.5	0.2
Nervous/Psychiatric		
dizziness	7.5	4.4

Table 1 Incidence of Adverse Reactions Occurring in Patients Treated with Lisinopril and hydrochlorothiazide In Controlled Clinical Trials

	Lisinopril Plus Hydrochlorothiazide n=930 (%)	Lisinopril n=2633 (%)
headache	5.2	5.6
paresthesia	1.5	0.5
vertigo	0.9	0.2
depression	0.5	0.7
somnolence	0.4	0.8
insomnia	0.2	0.3
Respiratory		
Cough	3.9	3.0
Upper respiratory infection	2.2	2.1
dyspnea	0.4	0.4

*see Lisinopril and hydrochlorothiazide (Marketing Experience Only)

Abnormal Hematologic and Clinical Chemistry Findings

Hypokalemia, Hyperkalemia: (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, and DRUG INTERACTIONS).

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (3.8%) and serum creatinine (4.2%) were observed in patients with essential hypertension treated with lisinopril and hydrochlorothiazide. More marked increases have also been reported and were more likely to occur in patients with bilateral renal artery stenosis. (see WARNINGS AND PRECAUTIONS, Renal).

Increases in blood urea nitrogen and serum creatinine, usually reversible upon discontinuation of therapy, were observed in 1.1 and 1.6% of patients respectively with essential hypertension treated with lisinopril alone.

Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglycerides and Calcium: (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 g percent and 1.5 vol percent, respectively) occurred frequently in hypertensive patients treated with lisinopril and hydrochlorothiazide but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, 0.4% of patients discontinued therapy due to anemia. Rarely, hemolytic anemia has been reported.

Agranulocytosis and bone marrow depression, manifested as anemia, cytopenia or leukopenia, have been caused by angiotensin converting enzyme inhibitors, including lisinopril. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded (see WARNINGS AND PRECAUTIONS, Hematologic).

Post-Market Adverse Drug Reactions

The following undesirable effects have been observed and reported during treatment with lisinopril and hydrochlorothiazide 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 lymphatic system disorders

Rare: anaemia.
Very rare: agranulocytosis, bone marrow depression, thrombocytopenia, leucopenia, hemolytic anaemia (see WARNINGS AND PRECAUTIONS, Hematologic).

Endocrine disorders

Rare: inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Uncommon: gout
Rare: hyperkalaemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism), hypokalaemia, hyperuricemia, hyperglycaemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Nervous system and psychiatric disorders

Common: dizziness, headache, paraesthesia.
Uncommon: depressive symptoms.
Rare: olfactory disturbance.

Cardiac and vascular disorders

Common: orthostatic effects **(**including hypotension), syncope.
Uncommon: palpitations.

Respiratory, thoracic and mediastinal disorders

Common: cough (see WARNINGS AND PRECAUTIONS, Ear/Nose/Throat).

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 Mylan-Lisinopril HCTZ who develop jaundice or marked elevation of hepatic enzymes should discontinue Mylan-Lisinopril HCTZ and receive appropriate medical follow up (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Skin and subcutaneous tissue disorders

Common: rash.

Uncommon: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see WARNINGS AND PRECAUTIONS, Immune).

Very rare: 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 manifestation 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 (see WARNINGS AND PRECAUTIONS, Renal), increases in liver enzymes (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic), decreases in haemoglobin.

Uncommon: decreases in haematocrit.

Rare: increases in serum bilirubin (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Other side effects reported with the individual components alone, and which may be potential side effects with Mylan-Lisinopril HCTZ, are:

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, sleep disturbance and hallucinations have been reported; bronchospasm, rhinitis, sinusitis, alopecia, urticaria, diapheresis, pruritis, psoriasis and severe skin disorders (including pemphigus, toxic epidermal necrolysis, Steven-Johnson Syndrome and erythema multiforme) have been reported; hyponatraemia, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, pancreatitis; rarely, haemolytic anaemia has been reported.

Hydrochlorothiazide

Anorexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis) (cutaneaous vasculitis), systemic lupus erythematosus, cutaneous lupus erythematosus, fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, hyperglycaemia, glycosuria, hyperuricemia, electrolyte imbalance including hyponatremia, muscle spasm, restlessness, transient blurred vision, renal failure, renal dysfunction and interstitial nephritis, acute myopia and acute angle-closure glaucoma.

DRUG INTERACTIONS

Drug-Drug Interactions

The drugs listed in Table 2 are based on either drug interaction case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
Agents Affecting Sympathetic Activity	CT	Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.	Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution.
Agents Causing Renin Release	CT	The antihypertensive effect of lisinopril and hydrochlorothiazide is augmented by antihypertensive agents that cause renin release (e.g. diuretics).	

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
Agents Increasing Serum Potassium	T	Since lisinopril decreases aldosterone production, elevation of serum potassium may occur.	Potassium-sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and with frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amantadine	C	Amantadine toxicity symptoms (ataxia, myoclonus confusion) occurred in a patient with parkinsonism previously stabilized on amantadine (300 mg daily), 7 days after starting treatment with triamterene and hydrochlorothiazide.	Amantadine toxicity is thought to be due to reduction of the tubular secretion.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Antacids	CT	Coadministration with antacids may decrease the oral bioavailability of ACE inhibitors due to delayed gastric emptying and/or elevated gastric pH.	The clinical significance of this interaction appears to be minor. As a precaution, patients may want to take ACE inhibitors and antacids or oral medications that contain antacids 1 to 2h apart.
Anticholinergic Agents, including atropine, biperiden, domperidone and metoclopramide.	T, CT	Anticholinergic agents may increase the absorption and oral bioavailability of thiazide diuretics. Pretreatment with propantheline prolonged T_{max} for hydrochlorothiazide from 2.4h to 4.8h and increased its total 48-hour urinary recovery by 36%. This may be associated with increased and prolonged antihypertensive	The proposed mechanism involves increased gastrointestinal transit time due to reduction of stomach and intestinal motility by anticholinergic agents. Blood pressure monitoring is recommended if concomitant administration is considered. Dose adjustment of lisinopril and hydrochlorothiazide may

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
		effect of hydrochlorothiazide. Similar results were reported for chlorothiazide in another study. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	be required.
Antidiabetic Agents (e.g. Insulin and oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar contriol. Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.
Antiepileptic Agents: Topiramate	CT	Thiazide diuretics such as chlorothiazide may enhance the hypokalemic effect of topiramate. Thiazide diuretics may increase the serum concentration of topiramate.	Monitor for increased topiramate concentrations/adverse effects (e.g., hypokalemia) with initiation/dose increase of a thiazide diuretic. Closely monitor serum potassium concentrations with concomitant therapy. Topiramate dose reductions may be necessary.
Carbamazepine	C	There may be an increased risk of symptomatic hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	The patient's mental status and serum sodium concentrations should be monitored periodically.
Antihypertensive Therapy	CT	When lisinopril is given to patients already treated with other antihypertensive agents, further falls in blood pressure may occur. Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, calcium channel blockers, ACEI, ARB, and direct rennin inhibitors).	Dose adjustments of other concomitantly taken antihypertensive may be required.

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
Antineoplastic drugs, including cyclophosphamide and methotrexate.	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects. Increased myelosuppression was reported when thiazides were coadministered with 5-Fluorouracil. Significant augmentation of granulocytopenia during thiazide-chemotherapy combination, as compared with chemotherapy without thiazides, was observed. The most consistent changes in the neutrophil count were observed during the period of maximal myelosuppression from the antitumor drugs. Antineoplastic-induced bone marrow suppression may be prolonged with concomitant thiazide administration. Thiazides have been associated with blood dyscrasias.	Hydrochlorothiazide was frequently part of drug interactions with anticancer drugs. The mechanism is unknown. Alternative antihypertensive therapy may be advisable. Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile Acid Sequestrants (e.g. cholestyramine and colestipol resins)	CT	Bile acid sequestrants bind hydrochlorothiazide in the gut and reduce its absorption from the gastrointestinal tract by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%.	Lisinopril and hydrochlorothiazide should be given at least 4h before or 4-6h after the administration of the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and Vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone. Coadministration with high doses of calcium and vitamin D supplements may potentiate the	Particularly susceptible patients include those with hyperparathyroidism, those treated for osteoporosis, and those receiving high dosages of vitamin D for hypoparathyroidism. Serum

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
		rise in serum calcium.	calcium should be monitored if thiazide diuretics are coadministered with high dosages of calcium and/or vitamin D. Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Capsaicin	CT	Capsaicin may worsen ACE inhibitor-induced cough.	
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia may occur.	Monitor serum potassium, and adjust medications, as required.
Cyclosporine	T	Coadministration may potentially result in hypermagnesemia, hyperuricemia, and increase risk of nephrotoxicity.	Renal function, serum electrolytes, uric acid levels, and cyclosporine blood concentrations should be monitored. The clinical significance is unknown.
Digoxin	CT	Hydrochlorothiazide may enhance the toxicity of digoxin and other digitalis glycosides by depleting serum-potassium concentrations. Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Caution should be used with concomitant administration of lisinopril and hydrochlorothiazide and digoxin. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or lisinopril and hydrochlorothiazide, as required.
Diuretic Therapy	CT	Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril.	The possibility of hypotensive effects with lisinopril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION). When lisinopril and hydrochlorothiazide is used,

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
			other diuretics are, as a rule unnecessary.
Dual blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs	CT	Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs or ACE inhibitors and aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment. Co-administration of ARBs, ACE inhibitors or aliskiren-containing drugs is generally not recommended in other patients, since each treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).
Gold	C	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.	
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The coadministration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of gout medications may be required.
Lithium	CT	Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of lisinopril and hydrochlorothiazide with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Nonsteroidal Anti-Inflammatory Drugs	CT	In some patients, the administration of a non-	When Lisinopril and hydrochlorothiazide and non-

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref.	Effect	Clinical comment
(NSAIDs)		steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. In some patients with compromised renal function, lisinopril coadministration with non-steroidal anti-inflammatory drugs (NSAIDS) may produce further renal function deterioration. Indomethacin may diminish the antihypertensive efficacy of concomitantly administered lisinopril and hydrochlorothiazide.	steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required. Patients with heart failure may be at particular risk.
Pressor Amines (e.g. norepinephrine)	CT	Possible decreased response to pressor amines but not sufficient to preclude their use.	
Rituximab used to treat cancer, transplant rejection, and some autoimmune diseases.	T, C	Antihypertensives such as chlorothiazide may enhance the hypotensive effect of rituximab.	Consider temporarily withholding antihypertensive medications for 12 hours prior to rituximab infusion to avoid excessive hypotension during or immediately after infusion.
Selective Serotonin Reuptake Inhibitors (SSRIs, e.g., citalopram, escitalopram, sertraline)	T,C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g., tubocurare	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants , such as curare derivatives.	
Tetracycline antibiotics	T,C	The coadministration of diuretics and tetracyclines may result in decreased renal function manifested by increases in serum creatinine and blood urea nitrogen (BUN).	Usually, no clinical intervention is necessary, unless decreases in renal function occur. If renal function deteriorates, discontinuation of one or both agents may be necessary.

Legend: C = Case Study; RCS= Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions
Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of Mylan-Lisinopril HCTZ (lisinopril and hydrochlorothiazide) should be determined by the titration of the individual components. Mylan-Lisinopril HCTZ should be taken at the same time each day.

Once the patient has been successfully titrated with the individual components as described below, either one Mylan-Lisinopril HCTZ 10/12.5 mg or one or two 20/12.5 mg or 20/25 mg tablets once daily may be substituted if the titrated doses are the same as those in the fixed combination. (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS).

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily, particularly when combined with antihypertensive agents.

Recommended Dose and Dosage Adjustment

Essential hypertension

For lisinopril monotherapy the recommended initial dose in patients not on diuretics is 10 mg of lisinopril once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range of lisinopril is 10 to 40 mg administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day.

If blood pressure is not controlled with lisinopril alone, a low dose of a diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of lisinopril.

Diuretic Treated Patients

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of lisinopril. The diuretic should if possible, be discontinued for two to three days before beginning therapy with lisinopril to reduce the

likelihood of hypotension (see WARNINGS AND PRECAUTIONS, Cardiovascular). The dosage of lisinopril should be adjusted according to blood pressure response.

If the patient's blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg of lisinopril alone should be administered and the patient remain under medical supervision for at least two hours, and until blood pressure has stabilized for at least an additional hour (see WARNINGS AND PRECAUTIONS, Cardiovascular and DRUG INTERACTIONS).

As a rule, concomitant diuretic therapy is not necessary when Mylan-Lisinopril HCTZ is used.

Dosage Adjustment in Renal Impairment

In patients with creatinine clearance greater than 30 mL/min the usual dose titration of the individual components is required.

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN] and during low density lipoproteins (LDL) apheresis with dextran sulphate and treated concomitantly with an ACE inhibitor. (see WARNINGS AND PRECAUTIONS, Immune).

For patients with creatinine clearance between 10 and 30 mL/min the starting dose of lisinopril is 2.5 - 5.0 mg/day. The dosage may then be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

When concomitant diuretic therapy is required in patients with severe renal impairment (creatinine clearance < 10 mL/min), a loop diuretic, rather than a thiazide diuretic is preferred for use with lisinopril. Therefore, for patients with severe renal dysfunction the lisinopril-hydrochlorothiazide combination tablet is not recommended.

Missed Dose

If the patient misses a dose, they should be advised not to take an extra dose to make up for the missed dose and just resume their usual schedule.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

No specific information is available on the treatment of overdosage with lisinopril and hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Mylan-Lisinopril HCTZ should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Lisinopril
Overdose symptoms include severe hypotension, electrolyte disturbances and renal failure. Overdosed patients should be kept under very close observation. Therapeutic measures depend on the nature and severity of symptoms. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, place the patient in the shock position and infuse intravenous normal saline immediately. Vasopressors including angiotensin II may be considered if fluid replacement is inadequate or contraindicated. Circulating lisinopril may be removed by hemodialysis. Avoid high-flux polyacrylonitrile dialysis membranes (see WARNINGS AND PRECAUTIONS, Immune). Serum electrolytes and creatinine should be monitored frequently.

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

ACTION AND CLINICAL PHARMACOLOGY

Lisinopril and hydrochlorothiazide combine the action of an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Mechanism of Action

Lisinopril

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion. Although the latter decrease is small, it results in a small increase in serum potassium. In patients treated with lisinopril plus a thiazide diuretic, there was essentially no change in serum potassium (see WARNINGS AND PRECAUTIONS). ACE is identical to kininase II. Thus, lisinopril may also block the degradation of bradykinin, a potent vasodilator peptide. However, the role that this plays in the therapeutic effects of lisinopril is unknown.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, lisinopril also lowers blood pressure

in patients with low-renin hypertension. However, black hypertensive patients (usually a low-renin hypertensive population) have a smaller average response to lisinopril monotherapy than non-black patients.

When lisinopril is given together with thiazide-type diuretics, its blood pressure lowering effect is approximately additive.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure. The mechanism of its antihypertensive action is not known. Lowering of the sodium content of arteriolar smooth muscle cells and diminished response to norepinephrine have been postulated.

Pharmacodynamics

Lisinopril

Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure. In most patients studied, after oral administration of an individual dose of lisinopril, the onset of antihypertensive activity is seen at one hour with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing. On occasion, achievement of optimal blood pressure reduction may require 2 to 4 weeks of therapy.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular

filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

Pharmacokinetics

Lisinopril

Absorption: Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. 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.

Based on urinary recovery, the extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6-60%) at all doses tested (5-80 mg).

Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Distribution: Lisinopril does not bind to plasma proteins other than ACE.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Metabolism: Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine.

Excretion: Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Lisinopril can be removed by dialysis.

Hydrochlorothiazide

Absorption: Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Metabolism: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney.

Excretion: The plasma half-life is 5.6-14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Lisinopril-Hydrochlorothiazide

Distribution: 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.

Special Populations and Conditions

Geriatrics: In a study in elderly healthy subjects (65 years and above), a single dose of lisinopril 20 mg produced higher serum concentrations and higher values for the area under the plasma curve than those seen in young healthy adults given a similar dose. In another study, single daily doses of lisinopril 5 mg were given for 7 consecutive days to young and elderly healthy volunteers. Maximum serum concentrations of lisinopril on Day 7 were higher in the elderly volunteers than in the young.

Renal Insufficiency: Impaired renal function decreases elimination of lisinopril. This decrease becomes clinically important when the glomerular filtration rate is below 30 mL/min. (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Store at controlled room temperature 15°C -30°C. Keep container tightly closed. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms
Mylan-Lisinopril HCTZ (lisinopril and hydrochlorothiazide) is available in tablets of 10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg strengths for oral administration.

Composition
Mylan-Lisinopril HCTZ tablets contain the active ingredients lisinopril (supplied as lisinopril dihydrate) and hydrochlorothiazide and the following non medicinal ingredients: dibasic calcium phosphate, magnesium stearate, mannitol, starch and talc. The 10 mg/12.5 mg and 20 mg/25 mg strengths also contain iron oxide yellow and iron oxide red.

Packaging
Mylan-Lisinopril HCTZ tablets are available in the following strengths and package sizes:

10/12.5 mg: Peach, round, biconvex tablet, debossed with “LHZT” over “10” on one side and “G” on the other side. **HDPE bottles of 100 and Unit Dose Cartons of 30**.

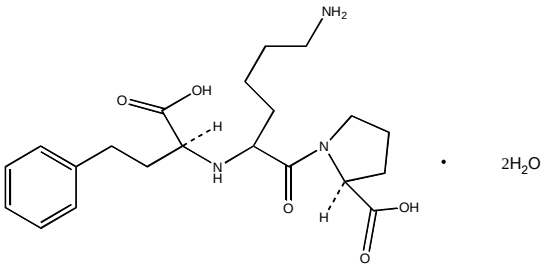
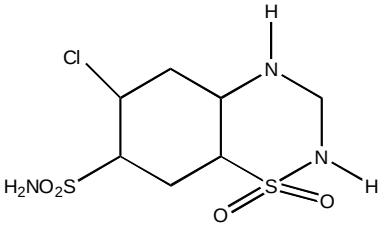
20/12.5 mg: White, round, biconvex tablet, debossed with “LHZT” over “20” on one side and “G” on the other side. **HDPE bottles of 100 and Unit Dose Cartons of 30**.

20/25 mg: Peach, round, biconvex tablet, debossed with “LHZT” over “20” on one side and “G” on the other side**. HDPE bottles of 100 and Unit Dose Cartons of 30.**

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names :	lisinopril	hydrochlorothiazide
Chemical Names:	(S0-1-[N-2-(1-carboxy-3-phenyl-propyl)-L-lysyl]-L-proline dihydrate	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
Structural Formulas:		
Molecular Formulas:	$C_{21}H_{31}N_3O_5\ 2H_2O$	$C_7H_8ClN_3O_4S_2$
Molecular Weights:	441.53 g/mol	297.72 g/mol
Description:	Lisinopril is a white to off-white, crystalline powder. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.	Hydrochlorothiazide is a white or practically white crystalline compound with low solubility in water, but is readily soluble in dilute aqueous sodium hydroxide.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, 2-way crossover bioequivalence study of Mylan-Lisinopril-HCTZ 20-25 mg tablets and Zestoretic® (lisinopril and hydrochlorothiazide) 20-25 mg tablets was performed in thirty-two (32/36) normal, healthy male subjects (age range = 18 – 45) under fasting conditions.

A summary of the comparative bioavailability data is presented below.

Lisinopril **1 x [20 mg (lisinopril)/25 mg (hydrochlorothiazide)]** **From measured data** **Geometric Mean** **Arithmetic Mean (CV %)**				
Parameter	**TEST***	**REFERENCE†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} ($ng \cdot h/mL$)	1123.15 1234.47 (45.86)	1300.79 1413.61 (38.90)	86	80 - 93
AUC_{0-inf} ($ng \cdot h/mL$)	1154.04 1261.94 (44.64)	1328.72 1438.12 (38.18)	87	81 - 94
C_{max} (ng/mL)	81.08 93.08 (54.44)	98.55 110.57 (45.97)	83	76 - 91
T_{max}§ (h)	6.81 (8.23)	6.80 (7.21)		
$T_{½}$§ (h)	12.36 (23.10)	10.97 (27.8)		

* Mylan-Lisinopril-HCTZ (lisinopril and hydrochlorothiazide) 20-25 mg Tablets (Mylan Pharmaceuticals ULC, Canada).

† Zestoretic® (lisinopril and hydrochlorothiazide) 20-25 mg Tablets by AstraZeneca Inc., Canada were purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only.

Hydrochlorothiazide 1 x [20 mg (lisinopril)/25 mg (hydrochlorothiazide)] From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**TEST***	**REFERENCE†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-t} (ng·h/mL)	995.28 1013.51 (19.40)	1060.80 1080.15 (19.93)	94	90 - 97
AUC_{0-inf} (ng·h/mL)	1028.62 1046.33 (18.83)	1097.48 1116.87 (19.69)	94	90 – 97
C_{max} (ng/mL)	168.90 176.09 (30.97)	163.35 171.65 (34.11)	103	95 - 113
T_{max}§ (h)	1.88 (34.71)	2.242 (39.50)		
$T_{½}$§ (h)	10.02 (14.32)	9.43 (13.00)		

* Mylan-Lisinopril-HCTZ (lisinopril and hydrochlorothiazide) 20-25 mg Tablets (Mylan Pharmaceuticals ULC., Canada).

† Zestoretic® (lisinopril and hydrochlorothiazide) 20-25 mg Tablets by AstraZeneca Inc., Canada were purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Lisinopril Pharmacology

	Species/strain	Number of animals/group	Route	Dose	Results
MECHANISM OF ACTION					
In vitro ACE inhibitory activity*	Hog plasma		*In vitro*		IC_{50} = 1.7 ± 0.5 M
Augmentation of contractile response to bradykinin	Guinea pig ileum	7 segments	*In vitro*		AC_{50} = 1.6 nM
In vivo ACE inhibition in the rat**	Male Sprague/Dawley	8	I.V.		ID_{50} = 2.3 (1.7-3.1) μg/kg
Duration of ACE Inhibitory activity of lisinopril in rats**	Male Sprague/Dawley	4	I.V.	3 & 10 μg/kg	Duration approx. 110 min.
In vivo ACE Inhibitory activity of lisinopril in conscious rats**	Sprague/Dawley	3 – 5	P.O.	0.03-3.0 mg/kg (single dose)	Duration of at least 360 min.
In vivo ACE inhibition in anesthetized dogs**	Mongrel	6	I.V.	1-30 μg/kg	ID_{50} = 6.5 μg/kg
In vivo ACE inhibitory activity of lisinopril in conscious dogs**	Mongrel	3	P.O.	0.05-1.0 mg/kg (single dose)	Duration of action between 6-24 hrs
EFFECTS ON BLOOD PRESSURE					
Antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel	3	P.O.	0.3 mg/kg with and without hydrochlorothiazide	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ = 11% reduction in mean systolic pressure vs. pretreatment.

	Species/strain	Number of animals/group	Route	Dose	Results
Antihypertensive activity in rats on a sodium-deficient diet (single doses)	Male Sprague/Dawley	5	P.O.	0.3 – 3.0 mg/kg daily for 4 days	After 2 hours: 11% reduction in mean systolic pressure vs pretreatment at 1 mg/kg. 22% reduction in mean systolic pressure vs. pretreatment at 3 mg/kg. Consistent response over 4 days.
Antihypertensive in 2 kidney Grollman hypertensive rats (single doses)	Male Sprague/Dawley	6 - 7	P.O.	1 & 3 mg/kg	At 2 hours: approx. 6% reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
Antihypertensive activity in spontaneously hypertensive rats with and without hydrochlorothiazide	SH rats	3-6	P.O.	1.25 mg/kg HCTZ=50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3 – 5 days. 2 hours after drug administration lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ the average mean arterial pressure was reduced from 202 to 132 mmHg.
Antihypertensive activity in spontaneously hypertensive rats (single doses)	SH rats	3-9	P.O. & I.V.	0.1 – 20 mg/kg	Slight fall in blood pressure at 0.312 – 5 mg/kg p.o. Pronounced fall at 20 mg/kg p.o. and 0.1 mg/kg I.V. with statistically significant reductions being observed for the majority of time points between ½ - 18 hours.

*Inhibition of enzymatic activity of hog plasma ACE using ^{14}C labelled substrate
**Blockage of functional (pressor) response to AI challenge

Hydrochlorothiazide Pharmacology

Hydrochlorothiazide increases the excretion of sodium and chloride in approximately equivalent amounts and causes a simultaneous, usually minimal loss of bicarbonate. The excretion of ammonia is reduced slightly by hydrochlorothiazide and the blood ammonia concentration may be increased. The excretion of potassium is increased slightly. Calcium excretion is decreased by hydrochlorothiazide and magnesium excretion is increased.

Hydrochlorothiazide is eliminated rapidly by the kidney. Its rate of elimination is decreased somewhat by the coadministration of probenecid without, however, an accompanying reduction in diuresis.

Lisinopril And Hydrochlorothiazide Pharmacology

In spontaneously hypertensive rats (SHR) lisinopril was studied in an oral dose of 1.25 mg/kg daily, given alone or concomitantly with hydrochlorothiazide 50 mg/kg orally, for 3 days. Reductions in blood pressure were recorded (tail cuff method) on each of the 3 treatment days, reaching normotensive levels (113-116 mmHg) on Day 3 at 4-8 hours after the concomitant therapy.

TOXICOLOGY

Lisinopril Toxicology

Acute Toxicity of Lisinopril

LD_{50} Values

Route	**Species**	**Sex**	**LD_{50} (g/kg)**
Oral	Mouse	Male	> 20
	Mouse	Female	> 20
	Rat	Male	> 20
	Rat	Female	> 20
	Dog	Male	> 6
	Dog	Female	> 6
Intravenous	Mouse	Male	> 10
	Mouse	Female	> 10
Intraperitoneal	Rat	Male	> 10
	Rat	Female	> 10

Signs of toxicity

Following oral administration to mice decreased activity and one male death (1/10) occurred. No signs of toxicity occurred in rats after oral administration. Dogs given 6 g/kg had transient

diarrhea and increases in serum urea nitrogen. Intravenous administration to mice produced bradypnea, ataxia, clonic convulsions, exophthalmia, and tremors. After intraperitoneal administration in rats, ataxia and one female death (1/10) occurred. No signs of toxicity or death occurred in the males.

Subacute/Chronic Toxicology (Lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Rat	2-Week	10 F + 10 M	Oral	3,10,30	At all doses, decrease of 2 to 16% in weight gain and 12 to 14% in heart weights were observed in female rats.
Rat	3-Month with 1-Month Interim	25 F + 25 M	Oral	3,10,30	At all doses, increased serum urea nitrogen values (up to approximately 2-fold) and decreased heart weights (7 to 10%) were observed in female rats. At 10 and 30 mg respectively weight gain decreased 11 to 14% in males. An increased incidence of focal erosions of the gastric mucosa and focal renal tubular basophilia were also seen.
Rat	1-Year with 6-Month Interim	25 F + 25 M	Oral	2,5,10,30,90[a]	At all doses, a decrease in weight gain (up to 16%) was observed. Serum urea nitrogen increased up to 4-fold; serum sodium decreased (average down to 3 mEq/L) and serum potassium increased (average up to 0.5 mEq/L). At 2, 5, 10 and 30 mg heart weight decreased; at 5, 10, and 30 mg, kidney weight increased; and at 5, 10, 30 and 90 mg, renal tubular basophilia increased. At 10, 30, and 90 mg, focal interstitial nephritis was observed.
Rat	3-Month with a 1-Month Interim and a 1-Month Recovery	30 F + 30 M	Oral	3,30,300,3000	At all doses, weight gain decreased by 5 to 11%, and increases were observed in serum urea nitrogen (up to approximately 3-fold) and serum potassium (average up to 0.4 mEq/L). At 30, 300 and 3000 mg there was an increased incidence of focal renal tubular basophilia and focal necrosis of the glandular mucosa of the stomach. An increased incidence of focal tubular basophilia persisted in rats given 300 or 3000 mg/kg/day.
Rat	1-Month	15 F + 15 M	Oral	30,60 30, 60 (with saline)	Saline supplementation prevented decreased weight gain and elevations in serum urea nitrogen at 30 and 60 mg. Decreases in cardiac weight at 30 and 60 mg, were suppressed by saline supplementation in males at 30 mg. At 30 and 60 mg renal changes produced due to a low salt diet (renal tubular degeneration and renal tubular basophilia) were prevented by saline supplementation. Mild gastric erosions or necrotic changes were seen in 1 or 2 of 30 rats given 30 or 60 mg. These gastric changes were not seen in saline supplemented animals given these doses; however, the relationship of amelioration due to saline is uncertain because of the low incidence of this change which is also occasionally seen in untreated animals.

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Rat	5 Days 6 Days Recovery	8 M	Oral	5, 300	Consumption of 2% saline increased during treatment at 5 mg and on Days 2 to 4 post-treatment at 300 mg.
Dog	2-Week	3 F + 3 M	Oral	3,10,30	At 30 mg, slight mineralization of the papilla muscle of the heart was seen in 1 of 6 dogs.
Dog	3-Month with 1-Month Interim	5 F + 5 M	Oral	3,10,30	At 10 mg hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums and gastric pyloric mucosa related to uremia. At 30 mg there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg average cardiac weight decreased (13 to 15%).
Dog	1 Year with 6 Month Interim	5 F + 5 M	Oral	3,5,15	At 15 mg, increases were observed in serum urea nitrogen (less than 2-fold). Decreases in serum-sodium (average down to 2 mEq/L) and increases in serum potassium (average up to 0.5 mEq/L) occurred at all doses.
Dog	18-Day	3 F + 3 M	Oral	60,90 with and without saline	Saline supplementation prevented increases in serum urea nitrogen in dogs given 60 mg for 6 days followed by 90 mg for 8 or 9 days.
Dog	7-Day	4 F + 4 M	i.v.	60,90	Decreases in blood pressure and increases in serum urea nitrogen occurred in dogs given 60 or 90 mg/kg/day. Supplementation with physiologic saline (25 mL/kg one hour prior to dosing and 4 hours after dosing) prevented these changes. Increased serum potassium (average up to 0.6 mEq/L) and decreased serum chloride (average down to 0.4 mEq/L) values were seen both in both supplemented and unsupplemented animals.

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Dog	1-Month	2 F + 2 M	Oral	3,30,300 and 1000	At 30 mg or greater, BUN increased and specific gravity of the urine decreased. Hyperplasia of renal epithelial cells were observed and deaths occurred. Dogs that died had dilation of distal renal tubules and fatty degeneration of renal tubular epithelium. No drug-related effects were observed at 3 mg.
Dog	3-Month with 1-Month Recovery (high dose)	Control 5 M + 5 F 3,10 & 30 mg/kg/day 3 M + 3 F 100 mg/kg/day 8 M + 8 F Recovery Control 2 M + 2 F 100 mg/kg/day 5 M + 5 F	Oral	3,10,30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.
Rabbit	2 Weeks	6 F	Oral	15 (1,6 & 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine, and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6 and 13 doses.

[a] Dosing terminated week 11, rats killed week 27.

Teratology Studies (Lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Mice	25	100, 300, 1000, 1000 with saline	Oral	Day 6 through Day 15 of gestation	No teratogenic effect was observed. There was an increased incidence of resorptions in all unsupplemented groups (no increase in serum urea nitrogen).
Rat	35	30, 100, 300, 300 with saline	Oral	Day 6 through Day 17 of gestation	No teratogenic effect was observed. Maternal weight gain decreased in all unsupplemented groups. The open field behavioral test (measure of spontaneous activity) showed increased activity in Week 5 postpartum F1 females at 300 mg with and without saline, but only in 300 mg with saline females in Week 6. When the open field test was repeated in males and females given 300 mg with and without saline in Week 11, no increase in activity was seen.
Rabbit (New Zealand)	18	0.1, 0.3, 1.0 all groups with saline	Oral	Day 6 through Day 18 of gestation	No teratogenic effect was observed. At all doses there was an increased incidence of incomplete ossification sternebrae, metacarpals, forefoot phalanges, pelvic bones and tali and/or calcanea) which was considered to represent a fetotoxic effect. At 1 mg one rabbit had a high incidence of resorptions.
Rabbit (New Zealand)	18	0.031, 0.125, 0.5	Oral	Day 6 through Day 18 of gestation	No fetotoxicity, nor embryotoxicity was observed at maternotoxic doses. At 0.125 and 0.5 mg maternal deaths, decreased maternal weight gain and food consumption, as well as increases in BUN, creatinine and potassium were seen. In addition, doses of 0.5 mg produced decreases in serum sodium and chloride, diffuse distention of the renal distal tubules and degeneration of renal tubules.

Fertility And Late Gestation And Lactation With Postnatal Evaluation Studies (Lisinopril)

Species	No. of Animals/Group	Route	Dose mg/kg/day	Duration of Dosing	Results
Rat	24 F & 24 M	Oral	30, 100, 300 300 with saline	Males were dosed for 78 days prior to mating and females from 15 days prior to mating until sacrifice on Day 20 of gestation.	Weight gain was reduced in unsupplemented males at all doses and during gestation in unsupplemented females. No effects on fertility and no signs of teratogenicity were observed. There was an increase in F1 pup deaths (3 to 8% vs. control 1%) Day 1 to 7 postpartum in 100 and 300 mg (saline and nonsaline) groups. Decreased mean F1 pup weight (3 to 7% less than controls) on Day 0 postpartum was seen in all unsupplemented groups.
Rat	20 F	Oral	30, 100, 300 300 with saline	Day 15 of gestation through Day 21 postpartum.	On Days 2 to 7 postpartum there was an increased number of dead pups (8 to 10% vs. control 0%). On Day 21 postpartum, a decrease in pup weights (8% less than controls) was observed in the unsupplemented 100 and 300 mg groups. There was no effect in the supplemented group. Pup development was not altered.

Genotoxicity Studies (Lisinopril)

Study	Test System	Dose	Results
Mutagenesis			
Microbial mutagen with and without metabolic activation	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100	up to 2000 µg/plate	Negative for mutagenic potential
	Escherichia coli WP2, WP2 uvrA	up to 10 mg/plate	
In vitro V-79 mammalian cell mutagenesis with and without metabolic activation	Chinese Hamster Lung Cell	up to 10 mM (4.42 mg/mL)	Negative for mutagenic potential
DNA Damage			
In vitro alkaline elution	Rat Hepatocyte	up to 30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks
Chromosomal Evaluation			
In vitro chromosomal aberration assay with and without metabolic activation	Chinese Hamster Ovary	up to 30 mM (13.25 mg/mL)	Negative for induction of chromosomal aberration
In vivo chromosomal aberration assay	Bone Marrow Cells of Male Mice	up to 5000 mg/kg	Negative for increases in chromosomal aberrations

Carcinogenicity Studies (Lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose Animals/Group	Results
Mice Cri: CD-1(ICR)BR	92 weeks	50 F & 50 M	Oral	15, 45, 135 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (7 to 15%) was seen in females at 135 mg. A greater incidence and severity of chronic nephritis in females and males given 45 and 135 mg was also seen.
Rats Cri:CD(SD)BR	105 weeks	50 F & 50 M	Oral	10, 30, 90 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (5 to 14%) in male drug-treated rats during the first 67 weeks of the study was observed. Focal sacculations of the retinal vessels was more prevalent in rats given 30 or 90 mg than in controls in Drug Week 100. An increased incidence of renal tubular hypertrophy in drug-treated males was seen at termination of the study (1 mg was considered the no-effect dose for this change in males based on an additional 105 week study at 1, 3, and 10 mg/kg/day). An increased incidence of chronic nephritis in drug-treated females (10 mg is the no-effect dose based on an additional 105 week study at 1, 3, and 10 mg/kg/day) was observed.

Hydrochlorothiazide Toxicology

Hydrochlorothiazide was found to have relatively low toxicity in acute and chronic toxicity studies. In acute animal toxicity studies in mice the LD_{50} was greater than 10,000 mg/kg suspension orally and was 884 mg/kg intravenously. In rats the acute LD_{50} was greater than 10,000 mg/kg suspension orally and 3,130 mg/kg suspension intraperitoneally. In the rabbit the acute intravenous LD_{50} was 461 mg/kg and in the dog it was approximately 1000 mg/kg. Dogs tolerated at least 2000 mg/kg orally without signs of toxicity.

Subacute oral toxicity studies in the rat at 500, 1000 and 2000 mg/kg/day of suspension five days a week for three weeks displayed no sign of drug effect. Three of the rats given 2000 mg/kg/day hydrochlorothiazide sodium salt died after the fifth day. These deaths were attributed to pneumonia. No sign of drug effect was observed among the other animals. In dogs given doses of 250, 500 and 1000 mg/kg seven days a week for 8 weeks, no gross signs of drug effect were noted except for electrolyte imbalance.

Chronic oral toxicity studies in the rat using doses of up to 2000 mg/kg/day 5 days per week for 26 weeks showed no signs of drug effect and no drug related changes on post mortem examination. In dogs oral doses of 0, 125, 250 mg/kg/day 5 days per week for 26 weeks; 500 mg/kg/day for 7 weeks; 11 weeks without drug then 500 mg/kg/day 7 days per week for 8 weeks, were given. Slight depression of plasma potassium, small amounts of yellow crystalline precipitate in the bladder in two of twelve dogs were found on gross examination. Histomorphologic studies did not show drug related changes.

Hydrochlorothiazide has been administered to rats in a two litter study, to mice in a two generation study, and to rabbits in an established pregnancy test. None of these studies showed any evidence of teratogenic effects of hydrochlorothiazide. Offspring carried on to weaning or maturity did not show evidence of effects related to treatment.

Toxicology (Lisinopril And Hydrochlorothiazide)

Species	Duration	No. of Animals/Group	Route	Dose	Effects
Rat	2-weeks	10 M + 10 F	Oral	Lisinopril, 0, 3, 10, 30 mg/kg/day; Lisinopril/HCTZ* 3/10, 10/10, 30/10 mg/kg/day	Decreased body weight gain was seen in all the drug-treated groups. A decrease in serum chloride occurred in all groups given the combination. Increased serum urea nitrogen occurred in the 2 highest groups given the combination. Renal tubular degeneration and gastritis or gastric ulcer occurred in one rat each at 10/10 and 30/10 mg/kg/day. An additional rat at 30/10 mg/kg/day also had a gastric ulcer without renal lesions. Decreased average heart weight (females) was seen in all the groups given the combination.
Rat	14-weeks	25 M + 25 F	Oral	Toxicity study with one month interim necropsy Lisinopril/HCTZ 0/0, 3/10, 10/10 30/10 mg/kg/day	Decreased body weight gain, increased serum urea nitrogen, decreased serum sodium and chloride, and decreased average heart weights, occurred at all dosage levels. Very slight focal necrosis of the fundic mucosa of the stomach occurred in the 2 highest dosage groups. Focal renal tubular basophilia occurred at a higher incidence in drug-treated animals compared to control animals.
Rat	27-weeks	15 M + 15 F	Oral	Lisinopril/HCTZ 0/0, 3/10, 10/10 30/10 mg/kg/day	All animals had average body weight gains approximately 5 to 25% below the controls throughout the study. Average serum nitrogen values were generally two to three times greater in drug-treated animals compared to controls. Other serum biochemical parameters changed very slightly. Decreases in erythrocyte parameters were seen at all dosage levels. Decreases in heart weight occurred at all dosage levels and increase in kidney weight occurred at the 2 highest dosage levels. Mineralization of the renal cortico-medullary junction occurred in 2 to 5 rats in each of the drug-treated groups. Very small or small necrotic foci of gastric mucosa occurred in 5 rats in the high dose group. Chronic nephritis and its early stage of renal tubular basophilia occurred among treated and control rats, but occurred at a greater incidence in treated rats.

Species	Duration	No. of Animals/Group	Route	Dose	Effects
Dog	2-weeks	3 M + 3 F	Oral	Lisinopril, 0, 3, 10, 30 mg/kg/day; Lisinopril/HCTZ 3/10, 10/10, 30/10 mg/kg/day	Average body weight losses in dogs given lisinopril 30 mg/kg/day or lisinopril 10 or 30 mg/kg/day with hydrochlorothiazide were probably related to treatment. Increase in serum urea nitrogen, creatinine and phosphorus occurred at the 2 highest dosage levels of the combination. At these doses renal tubular degeneration and secondary lymphoid depletion and gastrointestinal lesions were seen. At the highest dose increases in SGPT, alkaline phosphatase, potassium, and calcium and decreases in serum chloride, necrosis of hepatocytes, and mineralization of the papillary muscle of the heart were seen.
Dog	14-weeks	5 M + 5 F	Oral	Toxicity study with one month interim necropsy Lisinopril/HCTZ 0/0, 1/10, 3/10 10/10 mg/kg/day	3 dogs given 10/10 mg/kg/day of lisinopril/hydrochlorothiazide showed physical signs that were attributable to drug treatment; these included decreased activity, dehydration and anorexia. Marked increases in the serum concentrations of urea nitrogen (128.4 to 271.5 mg/100 mL), creatinine (5.1 to 11.5 mg/100 mL), and phosphorus (9.2 to >16.0 mg/100 mL) in terminal samples of 3 dogs given 10/10 mg/kg/day of lisinopril/hydrochlorothiazide that were sacrificed due to their poor physical condition after 11 or 18 doses. These dogs had renal tubular necrosis and secondary lymphoid depletion, and gastrointestinal lesions. At 3/10 mg/kg/day, an increase in serum urea nitrogen was seen. At all doses decreases in serum sodium, potassium, and chloride occurred probably due to hydrochlorothiazide.
Dog	27-weeks	3 M + 3 F	Oral	Lisinopril/HCTZ 0/0, 0.3/1, 1/3, 3/10 mg/kg/day	All dogs given 3/10 mg/kg/day had elevations in serum urea nitrogen and some had increases in serum creatinine. One dog at this level was markedly affected with increases in serum urea nitrogen, creatinine, glucose, GOT, and GPT and decreases in serum sodium, chloride, and potassium. This dog was killed in the fifth week and had renal tubular degeneration and secondary lymphoid depletion and gastrointestinal lesions. A transient decrease in blood erythroid parameters were seen at the highest dosage level and a decrease in serum sodium and at necropsy males in this group had a mild hypertrophy of the renal proximal tubules probably due to hypokalemia. The only changes seen at 0.3/1 and 1/3 mg/kg/day were decreases in serum potassium and chloride, and elevation in serum urea nitrogen at 1/3 mg/kg/day.

* Hydrochlorothiazide

Teratology (lisinopril and hydrochlorothiazide)

Species	Duration	No. of Animals/Group	Route	Dose	Effects
Mouse	4-weeks	25 F	Oral	Lisinopril/HCTZ 0/0, 10/10, 30/10, 90/10 mg/kg, 90/10 mg/kg + 0.9% Saline – Days 6 – 15 of Gestation	There were no maternal deaths and no treatment-related abortions. In all drug-treated groups there were no treatment-related effects on mean live fetal weights and numbers of implants and live and dead fetuses. There was a dose-response increase in incidence of skeletal malformations. In addition, there was an increase in the incidence of lumbar ribs, a skeletal-variation, among drug treated groups. All of the skeletal malformations, with the exception of the fetus with the extra vertebra, were among mice not given saline supplementation and have occurred at comparable incidences in control groups of other studies, and some were observed in the control group of this study. A repeat of this study did not produce any evidence of treatment-related fetal skeletal malformations.
Rat	4-weeks	25 F	Oral	Lisinopril/HCTZ 0/3, 10/10, 30/10, 90/10 mg/kg + 0.9% Saline – Days 6-17 of Gestation	In the lisinopril/hydrochlorothiazide 90/10 mg/kg/day group, there was a significant ($P \leq 0.05$) decrease in the number of live fetuses per pregnant female. Maternotoxicity was evident in all unsupplemented drug-treated groups. There were significant ($P \leq 0.05$) treatment-related decreases in live fetal weight in all drug-treated groups not supplemented with saline. Fetal weight in the 90/10 mg/kg/day group supplemented with saline was comparable to control. There was an increased incidence of fetuses with incompletely ossified sternebrae in the 30/10 and 90/10 mg/kg/day groups without saline supplementation which were considered to represent an embryotoxic effect. Ossification was not delayed in the 10/10 mg/kg/day group or the 90/10 mg/kg/day group supplemented with saline.
Rat	4-weeks	20 or 22 F	Oral	Lisinopril/HCTZ 0/0, 3/10, 30/10, 90/10 mg/kg + 0.9% Saline – Days 6-17 of Gestation	Fetotoxicity was apparent as treatment-related decreases in live fetal weight at all dosage levels without saline supplementation which were statistically significant ($P \leq 0.05$) in the 30/10 and 90/10 mg/kg/day groups. Results from this study confirmed those of the previous study. There was a delay in ossification, consistent with decreased live weights, at all dosage levels without saline supplementation. Maternotoxicity was evident in all unsupplemented drug-treated groups.

Mutagenicity

Lisinopril and Hydrochlorothiazide

The results of a battery of mutagenic and chromosomal aberration studies (Ames test, mammalian cell mutagenesis assay, an *in vitro* alkaline elution test for single strand DNA breaks, an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse bone marrow chromosome aberration) failed to reveal a genotoxic potential for the combination of lisinopril and hydrochlorothiazide.

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PART III: CONSUMER INFORMATION

[Pr]Mylan-Lisinopril HCTZ
Lisinopril and Hydrochlorothiazide Tablets, Mfr. Std
10 mg/12.5 mg, 20 mg/ 12.5 mg and 20 mg/25 mg

This leaflet is part III of a three-part "Product Monograph" published when Mylan-Lisinopril HCTZ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Mylan-Lisinopril HCTZ. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Mylan-Lisinopril HCTZ lowers high blood pressure.

What it does:
Mylan-Lisinopril HCTZ contains a combination of 2 drugs, lisinopril and hydrochlorothiazide:

- Lisinopril is an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in '-PRIL'. It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This lowers blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking Mylan-Lisinopril HCTZ regularly even if you feel fine.

When it should not be used:
Do not take Mylan-Lisinopril HCTZ if you:

- Are allergic to lisinopril, hydrochlorothiazide, or to any non-medicinal ingredient in the formulation.
- Are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-MIDE".
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors such as surgery, flu, or dental procedures.
- Have certain kidney diseases or have difficulty urinating or produce no urine.
- Are pregnant or intend to become pregnant. Taking Mylan-Lisinopril HCTZ during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. Lisinopril and hydrochlorothiazide passes into breast milk.

What the medicinal ingredients are:
Lisinopril and hydrochlorothiazide.

What the non-medicinal ingredients are:
Other inactive ingredients in Mylan-Lisinopril HCTZ include: Dibasic calcium phosphate, magnesium stearate, mannitol, starch and talc. The 10 mg/12.5 mg and 20 mg/25 mg strengths also contain iron oxide yellow and iron oxide red.

What dosage forms it comes in:
Lisinopril and hydrochlorothiazide tablets: 10 mg/12.5 mg, 20 mg/12.5 mg and 20 mg/25 mg

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS – Pregnancy

Mylan-Lisinopril HCTZ should not be used during pregnancy. If you discover that you are pregnant while taking Mylan-Lisinopril HCTZ, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use Mylan-Lisinopril HCTZ talk to your doctor, nurse, or pharmacist if you:

- Have experienced an allergic reaction to any drug used to lower blood pressure or penicillin.
- Have recently received or are planning to get allergy shots for bee or wasp stings or have an allergy.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Have lupus, gout, or asthma.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with Mylan-Lisinopril HCTZ is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-**SARTAN**"
- Are on a low-salt diet.
- Are on dialysis.
- Are receiving gold (sodium aurothiomalate) injections.
- Are less than 18 years old.

- Are on LDL Apheresis (a treatment to lower the LDL cholesterol in the blood).

Hydrochlorothiazide in Mylan-Lisinopril HCTZ can cause Sudden Eye Disorders:

- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting Mylan-Lisinopril HCTZ.

You may become sensitive to the sun while taking Mylan-Lisinopril HCTZ. Exposure to sunlight should be minimized until you know how you respond.

If you are going to have surgery and will be given an anesthetic, be sure to tell your doctor or dentist that you are taking Mylan-Lisinopril HCTZ.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to Mylan-Lisinopril HCTZ. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Mylan-Lisinopril HCTZ:

- Adrenocorticotropic hormone (ACTH) may be used to treat nephrotic syndrome and in diagnostic tests.
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amantadine used to treat the flu and reduce symptoms of Parkinson's disease.
- Amphotericin B, an antifungal drug.
- Antacids.
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), diazoxide, methyldopa and beta blockers such as atenolol, metoprolol, propranolol, calcium channel blockers such as felodipine, amlodipine, nifedipine, and angiotensin II receptor blockers such as candesartan, valsartan, losartan. When taken in combination with Mylan-Lisinopril HCTZ may cause excessively low blood pressure.
- Calcium or vitamin D supplements.
- Capsaicin, an ingredient in some creams used to relieve arthritis pain.
- Corticosteroids used to treat joint pain and swelling.
- Cyclosporine used to treat autoimmune diseases.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function, including atropine, biperiden, domperidone and metoclopramide.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gold (sodium aurothiomalate), used to treat auto-immune conditions such as rheumatoid arthritis and psoriatic arthritis.
- Gout medications, including allopurinol and probenecid.
- Lithium, a medicine to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Rituximab used to treat cancer, transplant rejection, and some autoimmune diseases.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare.
- Tetracycline antibiotics.

PROPER USE OF THIS MEDICATION

Take Mylan-Lisinopril HCTZ exactly as prescribed.

It is recommended to take your dose at about the same time everyday.

Mylan-Lisinopril HCTZ can be taken with or without food. If Mylan-Lisinopril HCTZ causes upset stomach, take it with food or milk.

Usual Adult Dose:
The dosage of Mylan-Lisinopril HCTZ is individualized and taken once a day.

It may be prescribed as follows:
One tablet of 10/12.5mg
Or,
One or two tablets of 20/12.5mg,
One or two tablets of 20/25mg

Overdose:

If you think you have taken too much Mylan-Lisinopril HCTZ contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately,

even if there are no symptoms.

Missed Dose:
If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- dizziness
- headache
- cough
- drowsiness, fatigue, weakness
- rash
- abdominal pain, upset stomach, decreased appetite, constipation
- muscle pain or cramps

If any of these affects you severely, tell your doctor, nurse or pharmacist.

Mylan-Lisinopril HCTZ can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical attention
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness may occur when you go from lying or sitting to standing up	√		
	Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		√	
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Kidney Disorder: decreased urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Increased blood sugar: frequent urination, thirst, and hunger	√		
	Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Rare	**Decreased Platelets:** bruising, bleeding, fatigue and weakness		√	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
Very Rare	**Toxic Epidermal Necrolysis:** severe skin peeling, especially in mouth and eyes			√
Unknown	**Eye disorders: -Myopia:** sudden near sightedness or blurred vision **- Glaucoma:** increased pressure in your eyes, eye pain			√
	Anemia: fatigue, loss of energy, weakness, shortness of breath		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		**Talk with your doctor, nurse, or pharmacist**		**Stop taking drug and seek immediate medical attention**
		Only if severe	**In all cases**	
	Inflammation of the pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		√	
	Hallucinations: sensation of seeing or hearing things		√	
	Lupus-like reactions: associated with fever, malaise, joint pains, myalgias, fatigues etc. May be activated, or lupus status may worsen		√	

This is not a complete list of side effects. For any unexpected effects while taking Mylan-Lisinopril HCTZ, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

- Store Mylan-Lisinopril HCTZ at controlled room temperature (15°C - 30°C). Keep container tightly closed. Protect from light.
- When you first open the package, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.
- Do not transfer Mylan-Lisinopril HCTZ to other pill containers.
- **Keep out of reach and sight of children**. Never take medicine in front of small children as they will want to copy you.
- Do not keep or use Mylan-Lisinopril HCTZ after the expiry date indicated on the package. Unused medicines, which you know you will no longer need, should be carefully discarded. You may wish to seek advice from your pharmacist.
- **Remember** to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- **Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);**
- **By calling 1-866-234-2345 (toll-free);**
- **By completing a Consumer Side Effect Reporting Form and sending it by:**
  - **Fax to 1-866-678-6789 (toll-free), or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC, at: 1-800-575-1379

This leaflet was prepared by Mylan Pharmaceuticals ULC, Etobicoke, Ontario, M8Z 2S6.

Revised on: December 01, 2014

Mylan

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