**July 29, 2024**

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

**Subject:** **ANDA Suitability Petition for Lisinopril and Hydrochlorothiazide Oral Liquid**

Dear Sir or Madam:

The undersigned submits this ANDA Suitability Petition pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and in accordance with 21 CFR § 10.20, §10.30, and §314.93. The Suitability Petition requests the FDA to confirm that Lisinopril and Hydrochlorothiazide Oral Liquid is suitable for submission in an Abbreviated New Drug Application (ANDA).

Please direct any questions regarding this submission to the undersigned below.

Sincerely,

Seth D. DePuy Digitally signed by Seth D. DePuy
Date: 2024.07.29 12:57:33 -04'00'

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**Drug Name:** **Lisinopril and Hydrochlorothiazide Oral Liquid**

**Indication:** **For the treatment of hypertension, to lower blood pressure**

# ANDA SUITABILITY PETITION

**Document Date: 29 July 2024**

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# 1 ACTION REQUESTED

The Suitability Petition requests that the FDA determine that the proposed fixed-dose Lisinopril and Hydrochlorothiazide Oral Liquid is suitable for submission as an Abbreviated New Drug Application (ANDA). This Suitability Petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetics Act and 21 CFR §314.93, is the appropriate mechanism for securing Food and Drug Administration authorization to submit an ANDA for a drug product that differs in dosage form from the Reference Listed Drug (RLD).

The RLD upon which the petition is based is: ZESTORETIC® (lisinopril; hydrochlorothiazide).

ZESTORETIC (NDA 019888) is marketed as an oral tablet and approved in the following dosage strengths:

| RLD Dosage Strength | Lisinopril | Hydrochlorothiazide |
|---|---|---|
| 1 | 10 mg | 12.5 mg |
| 2 | 20 mg | 12.5 mg |
| 3 | 20 mg | 25 mg |

The Petitioner's proposed Lisinopril and Hydrochlorothiazide product will be developed as an Oral Liquid at the same dosage strengths as the RLD:

| Proposed Dosage Strengths | Lisinopril | Hydrochlorothiazide | Proposed Formulation Lisinopril + Hydrochlorothiazide |
|---|---|---|---|
| 1 | 10 mg / 5 mL | 12.5 mg / 5 mL | 10 mg & 12.5 mg per 5 mL |
| 2 | 20 mg / 5 mL | 12.5 mg / 5 mL | 20 mg & 12.5 mg per 5 mL |
| 3 | 20 mg / 5 mL | 25 mg / 5 mL | 20 mg & 25 mg per 5 mL |

A copy of the currently approved ZESTORETIC product labeling is provided in Appendix 1. In addition, a copy of the relevant page from the current Electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for ZESTORETIC is provided as Appendix 2.

The drug, the route of administration and the recommendations for use are the same as the RLD product. The proposed drug product will differ from the marketed tablet products only in dosage form.

Approval of this Suitability Petition will allow the Petitioner to submit Lisinopril and Hydrochlorothiazide Oral Liquid as an ANDA and permit convenient dosing and administration by healthcare providers to treat patients with hypertension in accordance with the approved indications for ZESTORETIC.

## 2 STATEMENT OF GROUNDS

The FDC Act permits, at Section 505(j)(2)(A)(iii) and 21 CFR 314.93, the submission of an ANDA for a drug product that differs in dosage form from the RLD after FDA has approved a petition seeking permission to file such an application.

ZESTORETIC (lisinopril; hydrochlorothiazide) was approved on 20 July 1989 under NDA 019888 and is marketed as an oral tablet at 3 dosage strengths for the treatment of hypertension, to lower blood pressure (see Appendix 1 for approved product labeling).

The Petitioner proposes Lisinopril and Hydrochlorothiazide Oral Liquid to be approved for the same indication as ZESTORETIC oral tablets. Table 1 below presents the comparison between the approved RLD product and the proposed drug product.

**Table 1 Comparison of Approved Drug Product to Proposed Drug Product – Dosage Strengths**

| | **RLD Product: ZESTORETIC (NDA 019888; Almatica Pharma, Inc)** | **Proposed Lisinopril and HCTZ Product** |
|---|---|---|
| Dosage Form | Tablet | Liquid |
| Route of Administration | Oral | Oral |
| Dosage Strengths (Lisinopril; HCTZ) | • 10 mg; 12.5 mg<br>• 20 mg; 12.5 mg<br>• 20 mg; 25 mg | • 10 mg; 12.5 mg per 5 mL<br>• 20 mg; 12.5 mg per 5 mL<br>• 20 mg; 25 mg per 5 mL |

HCTZ = hydrochlorothiazide; NDA = New Drug Application; RLD = reference listed drug

**Approved Indication and Usage:**

Lisinopril and Hydrochlorothiazide (HCTZ) as a fixed-dose combination oral tablet product is approved for the treatment of hypertension, to lower blood pressure (Almatica Pharma Inc. (2020); see Appendix 1).

Lisinopril is a potent Angiotensin Converting Enzyme inhibitor. The mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system by preventing the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. HCTZ is a diuretic and antihypertensive that reduces the reabsorption of electrolytes in the distal tubule of the kidney leading to increases urine output and reduced blood volume, thus contributing to the lowering of blood pressure. Together, lisinopril and HCTZ provide a synergistic anti-hypertensive effect as lisinopril relaxes blood vessels and improves perfusion, whereas HCTZ reduces blood volume.

**Approved Dosage and Administration:**

ZESTORETIC is available at 3 dosage strengths (see Table 1). The appropriate oral tablet dose is titrated to clinical effect (Almatica Pharma Inc. (2020); see Appendix 1).

*A patient whose blood pressure is not adequately controlled with either lisinopril or hydrochlorothiazide monotherapy may be switched to lisinopril/HCTZ 10/12.5 or lisinopril/HCTZ 20/12.5, depending on current monotherapy dose. Further increases of either or both components should depend on clinical response with blood pressure measured at the interdosing interval to ensure that there is an adequate antihypertensive effect at that time.*

*Lisinopril monotherapy is an effective treatment of hypertension in once-daily doses of 10 mg to 80 mg, while hydrochlorothiazide monotherapy is effective in doses of 12.5 mg per day to 50 mg per day. In clinical trials of lisinopril/hydrochlorothiazide combination therapy using lisinopril doses of 10 mg to 80 mg and hydrochlorothiazide doses of 6.25 mg to 50 mg, the antihypertensive response rates generally increased with increasing dose of either component.*

**Proposed Indication/Usage, Dosage, and Administration:**

The proposed indication for Lisinopril and Hydrochlorothiazide Oral Liquid product will be consistent with the approved, labeled indication of the RLD (ZESTORETIC).

The proposed Lisinopril and Hydrochlorothiazide Liquid product is intended to be dosed by the same route (i.e., oral) as the RLD.

The proposed Lisinopril and Hydrochlorothiazide Oral Liquid product will be available in 3 dosage strengths (see Table 1). Importantly, these are the same approved dosage strengths as the RLD and will cover the same available dosing range as the RLD (see Table 2). Dosing instructions will remain consistent with the RLD.

**Table 2 Comparison of Approved Drug Product to Proposed Drug Product – Dosing Range**

| Dose (mg) [Lisinopril; HCTZ] | RLD Product: ZESTORETIC (NDA 019888; Almatica Pharma, Inc) | Proposed Lisinopril and HCTZ Product |
|---|---|---|
| 10; 12.5 | 1 tablet (10; 12.5) | 5 mL (10; 12.5) |
| 20; 12.5 | 1 tablet (20; 12.5) | 5 mL (20; 12.5) |
| 20; 25 | 1 tablet (20; 25) | 5 mL (20; 25) |
| 40; 25 | 2 tablets (20; 12.5) | 10 mL (20; 12.5) |
| 80; 50 | 4 tablets (20; 12.5) | 20 mL (20; 12.5) |

The proposed Lisinopril and Hydrochlorothiazide Oral Liquid product does not pose any new questions of Safety or Effectiveness since the proposed strengths are the same as that stated in the approved product labeling of the RLD approved under NDA 019888. The active ingredients, dosage regimen, uses and route of administration of the proposed strengths will be the same as applicable to the RLD. The Petitioner intends to conduct a study to establish bioequivalence to the RLD.

Draft labeling for the proposed Lisinopril and Hydrochlorothiazide Oral Liquid product is provided in Appendix 3.

## 3 ENVIRONMENTAL IMPACT

The Petitioner claims a categorical exclusion under 21 CFR 25.31.

## 4 ECONOMIC IMPACT STATEMENT

The Petitioner does not believe that this requirement is applicable at this time, but will agree to submit economic impact information, in accordance with 21 CFR 10.30(b), if requested by the Agency.

## 5 CERTIFICATION

The Petitioner certifies that to their best knowledge and belief, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

## 6 PEDIATRIC RESEARCH EQUITY ACT (PREA)

ANDAs submitted under an approved suitability petition for changes in dosage form, route of administration, or new active ingredient in fixed-combination products are subject to the pediatric assessment requirements that PREA imposes (21 USC 355B). As the proposed Lisinopril and Hydrochlorothiazide Oral Liquid product is a change in dosage from the currently approved ZESTORETIC oral tablet, PREA requirements are triggered.

The Petitioner believes that a pediatric assessment is not applicable to the proposed Lisinopril and Hydrochlorothiazide Oral Liquid product because the proposed change only facilitates the availability of the drug product in a liquid dosage form in place of a tablet dosage, while the active ingredients, indication, dosage strengths, route of administration and dosing regimen remain identical to that of the RLD, ZESTORETIC, as approved under NDA 019888 (Appendix 1).

Therefore, the Petitioner does not plan to submit any pediatric assessments with its application. A request for waiver of pediatric studies is included with this Petition.

# 7 REFERENCES

Almatica Pharma Inc. (2020). Approved product labeling for ZESTORETIC (hydrochlorothiazide + lisinopril); oral tablet; (NDA 019888). In *https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/019888s069lbl.pdf*.

# 8 APPENDICES

## APPENDIX 1: APPROVED PRODUCT LABELING – ZESTORETIC

# ZESTORETIC®
# (*lisinopril and hydrochlorothiazide*)

**WARNING: FETAL TOXICITY**

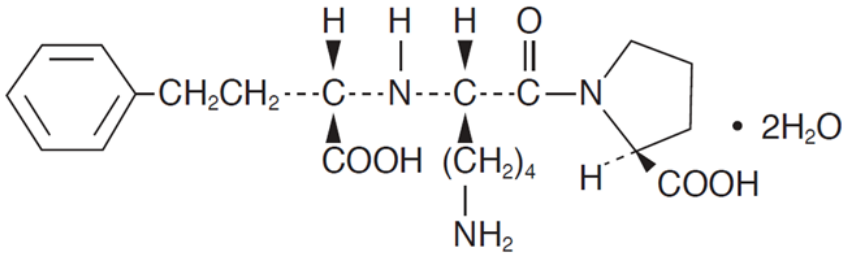
***See full prescribing information for complete boxed warning.***

- **When pregnancy is detected, discontinue ZESTORETIC as soon as possible.**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See Warnings: Fetal Toxicity.**

## DESCRIPTION

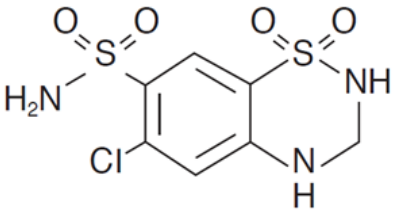
ZESTORETIC® (Lisinopril and Hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril, a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. It is chemically described as (S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ and its structural formula is:



Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53. It is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

ZESTORETIC is available for oral use in three tablet combinations of lisinopril with hydrochlorothiazide: ZESTORETIC 10-12.5 containing 10 mg lisinopril and 12.5 mg hydrochlorothiazide; ZESTORETIC 20-12.5 containing 20 mg lisinopril and 12.5 mg hydrochlorothiazide; and, ZESTORETIC 20-25 containing 20 mg lisinopril and 25 mg hydrochlorothiazide.

**Inactive Ingredients:**

10-12.5 Tablets - calcium phosphate, magnesium stearate, mannitol, red ferric oxide, corn starch, yellow ferric oxide.

20-12.5 Tablets - calcium phosphate, magnesium stearate, mannitol, corn starch.

20-25 Tablets - calcium phosphate, magnesium stearate, mannitol, red ferric oxide, corn starch, yellow ferric oxide.

## CLINICAL PHARMACOLOGY

### Lisinopril and Hydrochlorothiazide

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of lisinopril blocks the renin-angiotensin aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of lisinopril and hydrochlorothiazide was approximately additive. The ZESTORETIC 10-12.5 combination worked equally well in black and white patients. The ZESTORETIC 20-12.5 and ZESTORETIC 20-25 combinations appeared somewhat less effective in black patients, but relatively few black patients were studied. In most patients, the antihypertensive effect of ZESTORETIC was sustained for at least 24 hours.

In a randomized, controlled comparison, the mean antihypertensive effects of ZESTORETIC 20-12.5 and ZESTORETIC 20-25 were similar, suggesting that many patients who respond adequately to the latter combination may be controlled with ZESTORETIC 20-12.5 (See DOSAGE AND ADMINISTRATION).

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.

### Lisinopril

Mechanism of Action

Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was less than 0.1 mEq/L; however, approximately 15 percent of patients had increases greater than 0.5 mEq/L and approximately six percent had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril plus a thiazide diuretic showed essentially no change in serum potassium (See PRECAUTIONS).

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. Although lisinopril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to lisinopril monotherapy than nonblack patients.

Pharmacokinetics and Metabolism

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. Lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25 percent, with large intersubject variability (6% to 60%) at all doses tested (5 mg to 80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

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

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients (see DOSAGE AND ADMINISTRATION). In a multiple dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, the AUC increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients. Lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues; however, milk of lactating rats contains radioactivity following administration of $^{14}C$ lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pharmacodynamics

Administration of lisinopril to patients with hypertension results in a reduction of supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients (See WARNINGS).

In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by six hours.

In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy.

At recommended single daily doses, antihypertensive effects have been maintained for at least 24 hours, after dosing, although the effect at 24 hours was substantially smaller than the effect six hours after dosing.

The antihypertensive effects of lisinopril have continued during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure; nor with a significant overshoot of pretreatment blood pressure.

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.

In patients with renovascular hypertension lisinopril has been shown to be well tolerated and effective in controlling blood pressure (See PRECAUTIONS).

### Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

## INDICATIONS AND USAGE

ZESTORETIC is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including lisinopril and hydrochlorothiazide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

These fixed-dose combinations are not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

In using ZESTORETIC, consideration should be given to the fact that an angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that lisinopril does not have a similar risk (See WARNINGS).

In considering the use of ZESTORETIC, it should be noted that ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients (see WARNINGS, Lisinopril).

## CONTRAINDICATIONS

ZESTORETIC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

ZESTORETIC is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer ZESTORETIC within 36 hours of switching to or from sacubitril/valsartan, a neprilysin inhibitor (see WARNINGS).

Do not co-administer aliskiren with ZESTORETIC in patients with diabetes (see PRECAUTIONS, Drug Interactions).

## WARNINGS

### Lisinopril

***Anaphylactoid and Possibly Related Reactions:*** Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ZESTORETIC) may be subject to a variety of adverse reactions, some of them serious.

***Head and Neck Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors, including lisinopril. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients. ZESTORETIC should be promptly discontinued and the appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided (See ADVERSE REACTIONS).**

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy or a neprilysin inhibitor may be at increased risk for angioedema (see PRECAUTIONS).

***Intestinal Angioedema*:** Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

***Anaphylactoid Reactions During Desensitization:*** Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

***Anaphylactoid Reactions during Membrane Exposure:*** Thiazide-containing combination products are not recommended in patients with severe renal dysfunction. Sudden and potentially life-threatening

anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69®*) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

***Hypotension and Related Effects:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of lisinopril use in salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS).

Syncope has been reported in 0.8 percent of patients receiving ZESTORETIC. In patients with hypertension receiving lisinopril alone, the incidence of syncope was 0.1 percent. The overall incidence of syncope may be reduced by proper titration of the individual components (See PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

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. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of lisinopril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

***Leukopenia/Neutropenia/Agranulocytosis:*** Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of lisinopril are insufficient to show that lisinopril does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of leukopenia/neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

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

## Fetal Toxicity

**Pregnancy category D**

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue ZESTORETIC as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue ZESTORETIC, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to ZESTORETIC for hypotension, oliguria, and hyperkalemia. (See Precautions, Pediatric Use).

No teratogenic effects of lisinopril were seen in studies of pregnant rats, mice, and rabbits. On a mg/kg basis, the doses used were up to 625 times (in mice), 188 times (in rats), and 0.6 times (in rabbits) the maximum recommended human dose.

Lisinopril and Hydrochlorothiazide

Teratogenicity studies were conducted in mice and rats with up to 90 mg/kg/day of lisinopril (56 times the maximum recommended human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2.5 times the maximum recommended human dose). Maternal or fetotoxic effects were not seen in mice with the combination. In rats decreased maternal weight gain and decreased fetal weight occurred down to 3/10 mg/kg/day (the lowest dose tested). Associated with the decreased fetal weight was a delay in fetal ossification. The decreased fetal weight and delay in fetal ossification were not seen in saline-supplemented animals given 90/10 mg/kg/day.

When used in pregnancy, during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue ZESTORETIC as soon as possible (See Lisinopril, Fetal Toxicity).

**Hydrochlorothiazide**

**Acute Myopia and Secondary Angle-Closure Glaucoma:** Hydrochlorothiazide, a sulfonamide, can cause 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 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.

**Teratogenic Effects:** Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 mg/kg/day to 5.6 mg/kg/day (approximately 1 to 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

**Nonteratogenic Effects:** These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions have occurred in the adult.

### Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

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.

Sensitivity reactions 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.

Lithium generally should not be given with thiazides (See PRECAUTIONS, Drug Interactions, Lisinopril and Hydrochlorothiazide).

## PRECAUTIONS

### General

#### Lisinopril

**Aortic Stenosis/Hypertrophic Cardiomyopathy:** As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including lisinopril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin-converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of lisinopril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of lisinopril and/or discontinuation of the diuretic may be required.

**Evaluation of the hypertensive patient should always include assessment of renal function (See DOSAGE AND ADMINISTRATION).**

**Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1.4 percent of hypertensive patients treated with lisinopril plus hydrochlorothiazide. 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 include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. ZESTORETIC should be used cautiously, if at all, with these agents and with frequent monitoring of serum potassium (See PRECAUTIONS, Drug Interactions).

**Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, almost always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Hydrochlorothiazide**

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because lisinopril reduces the production of

aldosterone, concomitant therapy with lisinopril attenuates the diuretic-induced potassium loss (See PRECAUTIONS, Drug Interactions, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

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

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary 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 and triglyceride levels may be associated with thiazide diuretic therapy.

## Information for Patients

**Angioedema:** Angioedema, including laryngeal edema may occur at any time during treatment with angiotensin-converting enzyme inhibitors, including ZESTORETIC. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

**Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

**Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician.

**Leukopenia/Neutropenia:** Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of leukopenia/neutropenia.

**Pregnancy:** Female patients of childbearing age should be told about the consequences of exposure to ZESTORETIC during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

**Non-melanoma Skin Cancer:** Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

**NOTE:** As with many other drugs, certain advice to patients being treated with ZESTORETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

## Drug Interactions

**Lisinopril**

**Hypotension - Patients on Diuretic Therapy:** 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. If it is necessary to continue the diuretic, initiate therapy with lisinopril at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS, and DOSAGE AND ADMINISTRATION). When a diuretic is added to the therapy of a patient receiving lisinopril, an additional antihypertensive effect is usually observed (See DOSAGE AND ADMINISTRATION).

**Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):** In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including lisinopril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving lisinopril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including lisinopril, may be attenuated by NSAIDs.

## Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The VA NEPHRON trial enrolled 1448 patients with type 2 diabetes, elevated urinary-albumin-to-creatinine ratio, and decreased estimated glomerular filtration rate (GFR 30 mL/min to 89.9 mL/min), randomized them to lisinopril or placebo on a background of losartan therapy and followed them for a median of 2.2 years. Patients receiving the combination of losartan and lisinopril did not obtain any additional benefit compared to monotherapy for the combined endpoint of decline in GFR, end state renal disease, or death, but experienced an increased incidence of hyperkalemia and acute kidney injury compared with the monotherapy group.

In general, avoid combined use of RAS inhibitors, closely monitor blood pressure, renal function and electrolytes in patients on ZESTORETIC and other agents that affect the RAS.

Do not co-administer aliskiren with ZESTORETIC in patients with diabetes. Avoid use of aliskiren with ZESTORETIC in patients with renal impairment (GFR < 60 mL/min).

**Other Agents:** Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No meaningful clinically important pharmacokinetic interactions occurred when lisinopril was used concomitantly with propranolol, digoxin, or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of lisinopril.

**Agents Increasing Serum Potassium:** Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if lisinopril is administered concomitantly with lithium.

**mTOR (mammalian target of rapamycin) inhibitors**

Patients receiving coadministration of ACE inhibitor and mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema. (see WARNINGS)

**Neprilysin Inhibitors**

Patients taking concomitant neprilysin inhibitors may be at increased risk for angioedema. (see WARNINGS)

**Hydrochlorothiazide**

When administered concurrently the following drugs may interact with thiazide diuretics.

**Alcohol, barbiturates, or narcotics -** potentiation of orthostatic hypotension may occur.

**Antidiabetic drugs (oral agents and insulin) -** dosage adjustment of the antidiabetic drug may be required.

**Other antihypertensive drugs -** additive effect or potentiation.

**Cholestyramine and colestipol resins -** Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

**Corticosteroids, ACTH -** intensified electrolyte depletion, particularly hypokalemia.

**Pressor amines (e.g., norepinephrine) -** possible decreased response to pressor amines but not sufficient to preclude their use.

**Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) -** possible increased responsiveness to the muscle relaxant.

**Lithium -** should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with ZESTORETIC.

**Non-Steroidal Anti-inflammatory Drugs -** In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when ZESTORETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of ZESTORETIC is obtained.

**Gold:** Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ZESTORETIC.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

### Lisinopril and Hydrochlorothiazide

Lisinopril in combination with hydrochlorothiazide was not mutagenic in a microbial mutagen test using *Salmonella typhimurium* (Ames test) or *Escherichia coli* with or without metabolic activation or in a forward mutation assay using Chinese hamster lung cells. Lisinopril and hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, it did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

### Lisinopril

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times* the maximum daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when

lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximum human dose based on body surface area in mice.

*Calculations assume a human weight of 50 kg and human body surface area of 1.62$m^2$.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. This dose is 188 times and 30 times the maximum daily human dose based on mg/kg and mg/$m^2$, respectively.

**Hydrochlorothiazide**

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). These doses are 150 times and 12 times for mice and 25 times and 4 times for rats the maximum human daily dose based on mg/kg and mg/$m^2$, respectively. The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 mcg/mL to 1300 mcg/mL, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 mg/kg and 4 mg/kg, respectively, prior to conception and throughout gestation. In mice this dose is 25 times and 2 times the maximum daily human dose based on mg/kg and mg/$m^2$, respectively. In rats this dose is 1 times and 0.2 times the maximum daily human dose based on mg/kg and mg/$m^2$, respectively.

## Nursing Mothers

It is not known whether lisinopril is excreted in human milk. However, milk of lactating rats contains radioactivity following administration of $^{14}C$ lisinopril. In another study, lisinopril was present in rat milk at levels similar to plasma levels in the dams. Thiazides do appear in human milk. Because of the potential for serious adverse reactions in nursing infants from ACE inhibitors and hydrochlorothiazide, a

decision should be made whether to discontinue nursing and/or discontinue ZESTORETIC, taking into account the importance of the drug to the mother.

### Pediatric Use

Neonates with a history of in utero exposure to ZESTORETIC:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

Safety and effectiveness in pediatric patients have not been established.

### Geriatric Use

Clinical studies of ZESTORETIC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function.

## ADVERSE REACTIONS

ZESTORETIC has been evaluated for safety in 930 patients including 100 patients treated for 50 weeks or more.

In clinical trials with ZESTORETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with lisinopril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials (including open label extensions) with any combination of lisinopril and hydrochlorothiazide were: dizziness (7.5%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%) all of which were more common than in placebo-treated patients. Generally, adverse experiences were mild and transient in nature, but see WARNINGS regarding angioedema and excessive hypotension or syncope. Discontinuation of therapy due to adverse effects was required in 4.4% of patients principally because of dizziness, cough, fatigue and muscle cramps.

Adverse experiences occurring in greater than one percent of patients treated with lisinopril plus hydrochlorothiazide in controlled clinical trials are shown below.

**Percent of Patients in Controlled Studies**

| | Lisinopril and Hydrochlorothiazide (n=930) Incidence (discontinuation) | | Placebo (n=207) Incidence |
|---|---|---|---|
| Dizziness | 7.5 | (0.8) | 1.9 |
| Headache | 5.2 | (0.3) | 1.9 |
| Cough | 3.9 | (0.6) | 1.0 |
| Fatigue | 3.7 | (0.4) | 1.0 |
| Orthostatic Effects | 3.2 | (0.1) | 1.0 |
| Diarrhea | 2.5 | (0.2) | 2.4 |
| Nausea | 2.2 | (0.1) | 2.4 |
| Upper Respiratory Infection | 2.2 | (0.0) | 0.0 |
| Muscle Cramps | 2.0 | (0.4) | 0.5 |
| Asthenia | 1.8 | (0.2) | 1.0 |
| Paresthesia | 1.5 | (0.1) | 0.0 |
| Hypotension | 1.4 | (0.3) | 0.5 |
| Vomiting | 1.4 | (0.1) | 0.5 |
| Dyspepsia | 1.3 | (0.0) | 0.0 |
| Rash | 1.2 | (0.1) | 0.5 |
| Impotence | 1.2 | (0.3) | 0.0 |

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in controlled trials and rarer, serious, possibly drug-related events reported in marketing experience are listed below:

**Body as a Whole:** Chest pain, abdominal pain, syncope, chest discomfort, fever, trauma, virus infection. **Cardiovascular:** Palpitation, orthostatic hypotension. **Digestive:** Gastrointestinal cramps, dry mouth, constipation, heartburn. **Musculoskeletal:** Back pain, shoulder pain, knee pain, back strain, myalgia, foot pain. **Nervous/Psychiatric:** Decreased libido, vertigo, depression, somnolence. **Respiratory:** Common cold, nasal congestion, influenza, bronchitis, pharyngeal pain, dyspnea, pulmonary congestion, chronic sinusitis, allergic rhinitis, pharyngeal discomfort. **Skin:** Flushing, pruritus, skin inflammation, diaphoresis, cutaneous pseudolymphoma. **Special Senses:** Blurred vision, tinnitus, otalgia. **Urogenital:** Urinary tract infection.

**Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (See WARNINGS).

In rare cases, intestinal angioedema has been reported in post marketing experience.

**Hypotension:** In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (1.4%), orthostatic hypotension (0.5%), other orthostatic effects (3.2%). In addition syncope occurred in 0.8% of patients (See WARNINGS).

**Cough:** See PRECAUTIONS - Cough.

## Clinical Laboratory Test Findings

**Serum Electrolytes:** (See PRECAUTIONS).

**Creatinine, Blood Urea Nitrogen:** Minor reversible increases in blood urea nitrogen and serum creatinine were observed in patients with essential hypertension treated with ZESTORETIC. More marked increases have also been reported and were more likely to occur in patients with renal artery stenosis (See PRECAUTIONS).

**Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglycerides and Calcium:** (See PRECAUTIONS).

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

**Liver Function Tests:** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. (See WARNINGS, Hepatic Failure).

Other adverse reactions that have been reported with the individual components are listed below:

**Lisinopril -** In clinical trials adverse reactions which occurred with lisinopril were also seen with ZESTORETIC. In addition, and since lisinopril has been marketed, the following adverse reactions have been reported with lisinopril and should be considered potential adverse reactions for ZESTORETIC: **Body as a Whole:** Anaphylactoid reactions (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure), malaise, edema, facial edema, pain, pelvic pain, flank pain, chills; **Cardiovascular:** Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension), pulmonary embolism and infarction, worsening of heart failure, arrhythmias (including tachycardia, ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia, and premature ventricular contractions), angina pectoris, transient ischemic attacks, paroxysmal nocturnal dyspnea, decreased blood pressure, peripheral edema, vasculitis; **Digestive:** Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, Hepatic Failure), gastritis, anorexia, flatulence, increased salivation; **Endocrine:** Diabetes mellitus, inappropriate antidiuretic hormone secretion; **Hematologic:** Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia, and thrombocytopenia have been reported in which a causal relationship to lisinopril can not be excluded; **Metabolic:** Gout, weight loss, dehydration, fluid overload, weight gain; **Musculoskeletal:** Arthritis, arthralgia, neck pain, hip pain, joint pain, leg pain, arm pain, lumbago; **Nervous System/Psychiatric:** Ataxia, memory impairment, tremor, insomnia, stroke, nervousness, confusion, peripheral neuropathy (e.g., paresthesia, dysesthesia), spasm, hypersomnia, irritability; mood alterations (including depressive symptoms); hallucinations; **Respiratory:** Malignant lung neoplasms, hemoptysis, pulmonary edema, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngitis, rhinitis, rhinorrhea, chest sound abnormalities; **Skin:** Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, psoriasis, rare cases of other severe skin reactions, including toxic epidermal necrolysis and Stevens-Johnson Syndrome (causal relationship has not been established); **Special Senses:** Visual loss, diplopia, photophobia, taste alteration, olfactory disturbance; **Urogenital:** Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, breast pain.

**Miscellaneous:** A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

**Hydrochlorothiazide - Body as a Whole:** Weakness; **Digestive:** Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice) (See WARNINGS, Hepatic Failure), pancreatitis, sialoadenitis, constipation; **Hematologic:** Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia; **Musculoskeletal:** Muscle spasm; **Nervous System/Psychiatric:** Restlessness; **Renal:** Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); **Skin:** Erythema multiforme including Stevens-Johnson Syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; **Special Senses:** Xanthopsia; **Hypersensitivity:** Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

**Postmarketing Experience**

**Non-melanoma Skin Cancer**

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

**To report SUSPECTED ADVERSE REACTIONS, contact Almatica Pharma at 1-877-447-7979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for voluntary reporting of adverse reactions.**

## OVERDOSAGE

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

### Lisinopril

Following a single oral dose of 20 g/kg no lethality occurred in rats and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Lisinopril can be removed by hemodialysis (see WARNINGS, Anaphylactoid Reaction During Membrane Exposure).

### Hydrochlorothiazide

Oral administration of a single oral dose of 10 g/kg to mice and rats was not lethal. 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.

## DOSAGE AND ADMINISTRATION

Lisinopril monotherapy is an effective treatment of hypertension in once-daily doses of 10 mg to 80 mg, while hydrochlorothiazide monotherapy is effective in doses of 12.5 mg per day to 50 mg per day. In clinical trials of lisinopril/hydrochlorothiazide combination therapy using lisinopril doses of 10 mg to 80 mg and hydrochlorothiazide doses of 6.25 mg to 50 mg, the antihypertensive response rates generally increased with increasing dose of either component.

The side effects (see WARNINGS) of lisinopril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of lisinopril and hydrochlorothiazide may be associated with either or both dose-independent or dose-dependent side effects, but addition of lisinopril in clinical trials blunted the hypokalemia normally seen with diuretics.

To minimize dose-dependent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

**Dose Titration Guided by Clinical Effect:** A patient whose blood pressure is not adequately controlled with either lisinopril or hydrochlorothiazide monotherapy may be switched to lisinopril/HCTZ 10/12.5 or lisinopril/HCTZ 20/12.5, depending on current monotherapy dose. Further increases of either or both components should depend on clinical response with blood pressure measured at the interdosing interval to ensure that there is an adequate antihypertensive effect at that time. The hydrochlorothiazide dose should generally not be increased until 2 to 3 weeks have elapsed. After addition of the diuretic it may be possible to reduce the dose of lisinopril. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen may achieve similar or greater blood-pressure control without electrolyte disturbance if they are switched to lisinopril/HCTZ 10/12.5.

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

If the diuretic cannot be discontinued, an initial dose of 5 mg of lisinopril should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, Drug Interactions).

Concomitant administration of ZESTORETIC with potassium supplements, potassium salt substitutes or potassium-sparing diuretics may lead to increases of serum potassium (See PRECAUTIONS).

**Replacement Therapy:** The combination may be substituted for the titrated individual components.

**Use in Renal Impairment:** Regimens of therapy with lisinopril/HCTZ need not take account of renal function as long as the patient's creatinine clearance is >30 mL/min/1.7m$^2$ (serum creatinine roughly ≤3 mg/dL or 265 μmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so lisinopril/HCTZ is not recommended (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure).

## HOW SUPPLIED

**ZESTORETIC 10-12.5 Tablets:** Peach, round, biconvex, uncoated tablets identified with "141" debossed on one side and "ZESTORETIC" on the other side are supplied in bottles of 90 tablets (NDC 52427-435-90).

**ZESTORETIC 20-12.5 Tablets:** White, round, biconvex, uncoated tablets identified with "142" debossed on one side and "ZESTORETIC" on the other side are supplied in bottles of 90 tablets (NDC 52427-436-90).

**ZESTORETIC 20-25 Tablets:** Peach, round, biconvex, uncoated tablets identified with “145” debossed on one side and "ZESTORETIC" on the other side are supplied in bottles of 90 tablets (NDC 52427-437-90).

### Storage

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Protect from excessive light and humidity.

*AN69 is a registered trademark of Hospal Ltd.
ZESTORETIC is a trademark of Alvogen AZ IP Holdings LLC.

Distributed by:
Almatica Pharma, Inc.
Morristown, NJ 07960 USA

PI435-08
Rev. 08/2020

## APPENDIX 2: FDA ORANGE BOOK – ZESTORETIC (ACCESSED 18 JUNE 2024)

# Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

| Mkt.Status | Active Ingredient | Proprietary Name | Appl. No. | Dosage Form | Route | Strength | TE Code | RLD | RS | Applicant Holder |
|---|---|---|---|---|---|---|---|---|---|---|
| RX | HYDROCHLOROTHIAZIDE; LISINOPRIL | ZESTORETIC | N019888 | TABLET | ORAL | 12.5MG; 10MG | AB | RLD | | ALMATICA PHARMA LLC |
| RX | HYDROCHLOROTHIAZIDE; LISINOPRIL | ZESTORETIC | N019888 | TABLET | ORAL | 12.5MG; 20MG | AB | RLD | | ALMATICA PHARMA LLC |
| RX | HYDROCHLOROTHIAZIDE; LISINOPRIL | ZESTORETIC | N019888 | TABLET | ORAL | 25MG; 20MG | AB | RLD | | ALMATICA PHARMA LLC |

## APPENDIX 3 PROPOSED DRAFT LABELING FOR THE LISINOPRIL AND HYDROCHLOROTHIAZIDE ORAL LIQUID PRODUCT

**WARNING: FETAL TOXICITY**

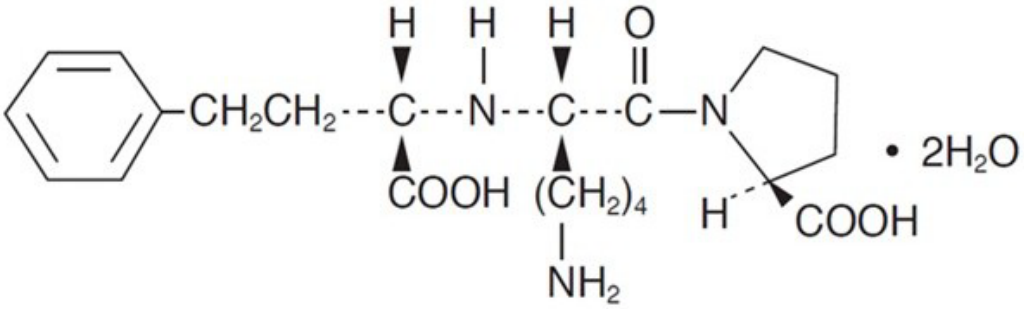
***See full prescribing information for complete boxed warning.***

- **When pregnancy is detected, discontinue Lisinopril and Hydrochlorothiazide Oral Liquid as soon as possible.**
- **Drugs that act directly on the renin-angiotensin system can causeinjury and death to the developing fetus. See Warnings: Fetal Toxicity.**

## DESCRIPTION

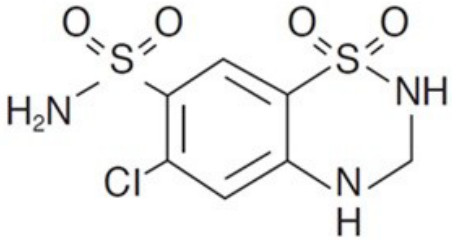
Lisinopril and Hydrochlorothiazide Oral Liquid combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril, USP a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. It is chemically described as (S)-1-[N2-(1-carboxy-3- phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \bullet 2H_2O$ and its structural formula is:



Lisinopril, USP is a white to off-white, crystalline powder, with a molecular weight of 441.53. It is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol.

Hydrochlorothiazide, USP is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide, USP is a white, or practically white, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Lisinopril and Hydrochlorothiazide Oral Liquid is available for oral use in three different combinations of lisinopril, USP with hydrochlorothiazide, USP:

- 10 mg + 12.5 mg/5 mL containing 10 mg lisinopril, USP and 12.5mg hydrochlorothiazide, USP
- 20 mg + 12.5 mg/5 mL containing 20 mg lisinopril, USP and 12.5 mg hydrochlorothiazide, USP
- 20 mg + 25 mg/5 mL containing 20 mg lisinopril, USP and 25 mg hydrochlorothiazide, USP

**Inactive Ingredients:**

Sodium Benzoate, Sorbitol, Glycerol, Citric Acid, Sodium Citrate, Purified water, Propylene Glycol, Poly-L-lysine, Hydroxyethyl cellulose, Strong Peppermint flavour, Orange flavour and Citrus flavour.

## CLINICAL PHARMACOLOGY

### Lisinopril and Hydrochlorothiazide

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of lisinopril blocks the renin-angiotensin aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of lisinopril and hydrochlorothiazide was approximately additive. The lisinopril and hydrochlorothiazide 10-12.5 combination worked equally well in black and white patients. The lisinopril and hydrochlorothiazide 20-12.5 and lisinopril and hydrochlorothiazide 20-25 combinations appeared somewhat less effective in black patients, but relatively few black patients were studied. In most patients, the antihypertensive effect of the lisinopril and hydrochlorothiazide combination was sustained for at least 24 hours.

In a randomized, controlled comparison, the mean antihypertensive effects of lisinopril and

hydrochlorothiazide 20-12.5 and lisinopril and hydrochlorothiazide 20-25 were similar, suggesting that many patients who respond adequately to the latter combination may be controlled with lisinopril and hydrochlorothiazide 20-12.5 (See DOSAGE AND ADMINISTRATION)

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

**Lisinopril**

Mechanism of Action

Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was less than 0.1 mEq/L; however, approximately 15 percent of patients had increases greater than 0.5 mEq/L and approximately six percent had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril plus a thiazide diuretic showed essentially no change in serum potassium (see PRECAUTIONS).

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. Although lisinopril was antihypertensive in a races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to lisinopril monotherapy than nonblack patients.

Pharmacokinetics and Metabolism

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. Lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25 percent, with large intersubject variability (6% to 60%) at a l doses tested (5 mg to 80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

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

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 mL/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients (see DOSAGE AND ADMINISTRATION). In a multiple dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, the AUC increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients. Lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues; however, milk of lactating rats contains radioactivity following administration of $^{14}C$ lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pharmacodynamics

Administration of lisinopril to patients with hypertension results in a reduction of supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients (see WARNINGS).

In most patients studied, onset of antihypertensive activity was seen at one hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by six hours.

In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy.

At recommended single daily doses, antihypertensive effects have been maintained for at least 24 hours, after dosing, although the effect at 24 hours was substantially smaller than the effect six hours after dosing.

The antihypertensive effects of lisinopril have continued during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure; nor with a significant overshoot of pretreatment blood pressure.

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.

In patients with renovascular hypertension, lisinopril has been shown to be well tolerated and effective in controlling blood pressure (see PRECAUTIONS).

**Hydrochlorothiazide**

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not

usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

## INDICATIONS AND USAGE

Lisinopril and Hydrochlorothiazide Oral Liquid is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classesincluding lisinopril and hydrochlorothiazide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce

cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) inblack patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

These fixed-dose combinations are not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

In using Lisinopril and Hydrochlorothiazide Oral Liquid, consideration should be given to the fact that an angiotensin- converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that lisinopril does not have a similar risk (see WARNINGS).

In considering the use of Lisinopril and Hydrochlorothiazide Oral Liquid it should be noted that ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients (see WARNINGS, Lisinopril).

## CONTRAINDICATIONS

Lisinopril and Hydrochlorothiazide Oral Liquid is contraindicated in patients who are hypersensitive to this product and inpatients with a history of angioedema related to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Lisinopril and Hydrochlorothiazide Oral Liquid is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer Lisinopril and Hydrochlorothiazide Oral Liquid within 36 hours of switching to or from sacubitril/valsartan, a neprilysin inhibitor (see WARNINGS).

Do not co-administer aliskiren with Lisinopril and Hydrochlorothiazide Oral Liquid in patients with diabetes (see PRECAUTIONS, Drug Interactions).

## WARNINGS

### Lisinopril

***Anaphylactoid and Possibly Related Reactions:*** Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lisinopril and Hydrochlorothiazide Oral Liquid) may be subject to a variety of adverse reactions, some of them serious.

***Head and Neck Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors, including lisinopril. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients. Lisinopril and Hydrochlorothiazide Oral Liquid should be promptly discontinued and the appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not

be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided (see ADVERSE REACTIONS).**

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy or a neprilysin inhibitor may be at increased risk for angioedema (see PRECAUTIONS).

***Intestinal Angioedema:*** Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

***Anaphylactoid Reactions During Desensitization:*** Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

***Anaphylactoid Reactions during Membrane Exposure:*** Thiazide-containing combination products are not recommended in patients with severe renal dysfunction. Sudden and potentially life-threatening anaphylactoid reactions have been reported in some

patients dialyzed with high-flux membranes (e.g., AN69®*) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be initiated.

Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane ora different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

***Hypotension and Related Effects:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of lisinopril use in salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis (see PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS).

Syncope has been reported in 0.8 percent of patients receiving lisinopril and hydrochlorothiazide. In patients with hypertension receiving lisinopril alone, the incidence of syncope was 0.1 percent. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

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. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of lisinopril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a

contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

***Leukopenia/Neutropenia/Agranulocytosis:*** Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of lisinopril are insufficient to show that lisinopril does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of leukopenia/neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

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

**Fetal Toxicity**

**Pregnancy category D**

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lisinopril and Hydrochlorothiazide Oral Liquid as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Mostepidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of thepotential risk to the fetus. Perform serial ultrasound examinations to assess the intra- amniotic environment. If oligohydramnios is observed, discontinue Lisinopril and Hydrochlorothiazide Oral Liquid, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Lisinopril and Hydrochlorothiazide Oral Liquid for hypotension, oliguria, and hyperkalemia. (See Precautions, Pediatric Use).

No teratogenic effects of lisinopril were seen in studies of pregnant rats, mice, and rabbits. On a mg/kg basis, the doses used were up to 625 times (in mice), 188 times (in rats), and 0.6 times (in rabbits) the maximum recommended human dose.

Lisinopril and Hydrochlorothiazide

Teratogenicity studies were conducted in mice and rats with up to 90 mg/kg/day of lisinopril (56 times the maximum recommended human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2.5 times the maximum recommended human dose). Maternal or fetotoxic effects were not seen in mice with the combination. In rats decreased maternal weight gain and decreased fetal weight occurred down to 3/10 mg/kg/day (the lowest dose tested). Associated with the decreased fetal weight was a delay in fetal ossification. The decreased fetal weight and delay in fetal ossification werenot seen in saline-supplemented animals given 90/10 mg/kg/day.

When used in pregnancy, during the second and third trimesters, ACE inhibitors cancause injury and even death to the developing fetus. When pregnancy is detected, discontinue Lisinopril and Hydrochlorothiazide Oral Liquid as soon as possible (see Lisinopril, Fetal Toxicity).

**Hydrochlorothiazide**

**Acute Myopia and Secondary Angle-Closure Glaucoma:** Hydrochlorothiazide, a

sulfonamide, can cause 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 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.

**Teratogenic Effects:** Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of externalabnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 mg/kg/day to 5.6 mg/kg/day (approximately 1 to 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

**Nonteratogenic Effects:** These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions have occurred in the adult.

**Hydrochlorothiazide**

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may developin patients with impaired renal function.

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.

Sensitivity reactions may occur in patients with or without a history of allergy orbronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Lisinopril and Hydrochlorothiazide).

## PRECAUTIONS

### General

### Lisinopril

**Aortic Stenosis/Hypertrophic Cardiomyopathy:** As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including lisinopril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin-converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of lisinopril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of lisinopril and/or discontinuation of the diuretic may be required.

**Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).**

**Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1.4 percent of hypertensive patients treated with lisinopril plus hydrochlorothiazide. 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 include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. Lisinopril and Hydrochlorothiazide Oral Liquid should be used cautiously, if at all with these agents and with frequent monitoring of serum potassium (see PRECAUTIONS, Drug Interactions).

**Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, almost always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Hydrochlorothiazide**

Periodic determination of serum electrolytes to detect possible electrolyte imbalanceshould be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis ispresent, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because lisinopril reduces the production of aldosterone, concomitant therapy with lisinopril attenuates the diuretic-induced potassium loss (see PRECAUTIONS, Drug Interactions, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

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

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary 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 and triglyceride levels may be associated with thiazide diuretic therapy.

**Information for Patients**

**Angioedema:** Angioedema, including laryngeal edema may occur at any time during treatment with angiotensin-converting enzyme inhibitors, including Lisinopril and Hydrochlorothiazide Oral Liquid. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with theprescribing physician.

**Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.
All patients should be cautioned that excessive perspiration and dehydration may lead toan excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

**Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician.

**Leukopenia/Neutropenia:** Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of leukopenia/neutropenia.

**Pregnancy:** Female patients of childbearing age should be told about the consequencesof exposure to Lisinopril and Hydrochlorothiazide Oral Liquid during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

**Non-melanoma Skin Cancer:** Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

**NOTE:** As with many other drugs, certain advice to patients being treated with Lisinopril and Hydrochlorothiazide Oral Liquid is warranted. This information is intended to aid in the safe and effectiveuse of this medication. It is not a disclosure of all possible adverse or intended effects.

## Drug Interactions

### Lisinopril

**Hypotension - Patients on Diuretic Therapy:** 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 discontinuingthe diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. If itis necessary to continue the diuretic, initiate therapy with lisinopril at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS,and DOSAGE AND ADMINISTRATION). When a diuretic is added to the therapy of a patient receiving lisinopril, an additional antihypertensive effect is usually observed (see DOSAGE AND ADMINISTRATION).

**Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):** In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including lisinopril, mayresult in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving

lisinopril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including lisinopril, may be attenuated by NSAIDs.

**Dual Blockade of the Renin-Angiotensin System (RAS)**

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskirenis associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The VA NEPHRON trial enrolled 1448 patients with type 2 diabetes, elevated urinary-albumin-to-creatinine ratio, and decreased estimated glomerular filtration rate (GFR 30mL/min to 89.9 mL/min), randomized them to lisinopril or placebo on a background of losartan therapy and followed them for a median of 2.2 years. Patients receiving the combination of losartan and lisinopril did not obtain any additional benefit compared to monotherapy for the combined endpoint of decline in GFR, end state renal disease, or death, but experienced an increased incidence of hyperkalemia and acute kidney injurycompared with the monotherapy group.

In general, avoid combined use of RAS inhibitors, closely monitor blood pressure, renal function and electrolytes in patients on Lisinopril and Hydrochlorothiazide Oral Liquid and other agents that affect the RAS.

Do not co-administer aliskiren with Lisinopril and Hydrochlorothiazide Oral Liquid in patients with diabetes. Avoid use of aliskiren with Lisinopril and Hydrochlorothiazide Oral Liquid in patients with renal impairment (GFR < 60 mL/min).

**Other Agents:** Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No meaningful clinically important pharmacokinetic interactions occurred when lisinopril was used concomitantly with propranolol, digoxin, or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of lisinopril.

**Agents Increasing Serum Potassium:** Lisinopril attenuates potassium loss causedby thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

**Lithium:** Lithium toxicity has been reported in patients receiving lithium concomitantlywith drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicitywas usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if lisinopril is administered concomitantly with lithium.

**mTOR (mammalian target of rapamycin) inhibitors**

Patients receiving coadministration of ACE inhibitor and mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see WARNINGS).

**Neprilysin Inhibitors**

Patients taking concomitant neprilysin inhibitors may be at increased risk forangioedema (see WARNINGS).

**Hydrochlorothiazide**

When administered concurrently the following drugs may interact with thiazide diuretics.

**Alcohol, barbiturates, or narcotics -** potentiation of orthostatic hypotension mayoccur.

**Antidiabetic drugs (oral agents and insulin) -** dosage adjustment of the antidiabetic drug may be required.

**Other antihypertensive drugs -** additive effect or potentiation.

**Cholestyramine and colestipol resins -** Absorption of hydrochlorothiazide isimpaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

**Corticosteroids, ACTH -** intensified electrolyte depletion, particularly hypokalemia.

**Pressor amines (e.g., norepinephrine) -** possible decreased response to pressoramines but not sufficient to preclude their use.

**Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) -** possible increased responsiveness to the muscle relaxant.

**Lithium -** should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Lisinopril and Hydrochlorothiazide Oral Liquid.

**Non-Steroidal Anti-inflammatory Drugs -** In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Lisinopril and Hydrochlorothiazide Oral Liquid and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of Lisinopril and Hydrochlorothiazide Oral Liquid is obtained.

**Gold:** Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including Lisinopril and Hydrochlorothiazide Oral Liquid.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Lisinopril and Hydrochlorothiazide**

Lisinopril in combination with hydrochlorothiazide was not mutagenic in a microbial

mutagen test using Salmonella typhimurium (Ames test) or Escherichia coli with or without metabolic activation or in a forward mutation assay using Chinese hamster lung cells. Lisinopril and hydrochlorothiazide did not produce DNA single strand breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, it did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow.

**Lisinopril**

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times* the maximum daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximumhuman dose based on body surface area in mice.

*Calculations assume a human weight of 50 kg and human body surface area of1.62$m^2$.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases inchromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. This dose is 188 times and 30 times themaximum daily human dose based on mg/kg and mg/$m^2$, respectively.

**Hydrochlorothiazide**

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of

hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) orin male and female rats (at doses of up to approximately 100 mg/kg/day). These dosesare 150 times and 12 times for mice and 25 times and 4 times for rats the maximum human daily dose based on mg/kg and $mg/m^2$, respectively. The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity)and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 mcg/mL to 1300 mcg/mL, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sexin studies wherein these species were exposed, via their diet, to doses of up to 100 mg/kg and 4 mg/kg, respectively, prior to conception and throughout gestation. Inmice this dose is 25 times and 2 times the maximum daily human dose based on mg/kgand $mg/m^2$, respectively. In rats this dose is 1 times and 0.2 times the maximum daily human dose based on mg/kg and $mg/m^2$, respectively.

**Nursing Mothers**

It is not known whether lisinopril is excreted in human milk. However, milk of lactating rats contains radioactivity following administration of $^{14}C$ lisinopril. In another study, lisinopril was present in rat milk at levels similar to plasma levels in the dams. Thiazides do appear in human milk. Because of the potential for serious adverse reactions in nursing infants from ACE inhibitors and hydrochlorothiazide, a decision should be made whether to discontinue nursing and/or discontinue Lisinopril and Hydrochlorothiazide Oral Liquid, taking into account the importance of the drug to the mother.

**Pediatric Use**

Neonates with a history of in utero exposure to Lisinopril and Hydrochlorothiazide Oral Liquid:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Clinical studies of lisinopril and hydrochlorothiazide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should becautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseaseor other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessmentof renal function.

## ADVERSE REACTIONS

Lisinopril and hydrochlorothiazide has been evaluated for safety in 930 patients including 100 patients treated for 50 weeks or more.

In clinical trials with lisinopril and hydrochlorothiazide no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with lisinopril or

hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials (including open label extensions) with any combination of lisinopril and hydrochlorothiazide were: dizziness (7.5%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%) all of which were more common than in placebo-treated patients. Generally, adverse experiences were mild and transient in nature, but see WARNINGS regarding angioedema and excessive hypotension or syncope. Discontinuation of therapy due to adverse effects was required in 4.4% of patients principally because of dizziness, cough, fatigue and muscle cramps.
Adverse experiences occurring in greater than one percent of patients treated with lisinopril plus hydrochlorothiazide in controlled clinical trials are shown below.

**Percent of Patients in Controlled Studies**

| | **Lisinopril and Hydrochlorothiazide (n=930) Incidence (discontinuation)** | **Placebo (n=207) Incidence** |
|---|---|---|
| **Dizziness** | 7.5 (0.8) | 1.9 |
| **Headache** | 5.2 (0.3) | 1.9 |
| **Cough** | 5.9 (0.6) | 1.0 |
| **Fatigue** | 3.7 (0.4) | 1.0 |
| **Orthostatic Effects** | 3.2 (0.1) | 1.0 |
| **Diarrhea** | 2.5 (0.2) | 2.4 |
| **Nausea** | 2.2 (0.1) | 2.4 |
| **Upper Respiratory Infection** | 2.2 (0.0) | 0.0 |
| **Muscle Cramps** | 2.0 (0.4) | 0.5 |
| **Asthenia** | 1.8 (0.2) | 1.0 |
| **Paresthesia** | 1.5 (0.1) | 0.0 |
| **Hypotension** | 1.4 (0.3) | 0.5 |
| **Vomiting** | 1.4 (0.1) | 0.5 |
| **Dyspepsia** | 1.3 (0.0) | 0.0 |
| **Rash** | 1.2(0.1) | 0.5 |
| **Impotence** | 1.2 (0.3) | 0.0 |

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in controlled trials and rarer, serious, possibly drug-related events reported in marketing experience are listed below:

**Body as a Whole:** Chest pain, abdominal pain, syncope, chest discomfort, fever,trauma, virus infection. **Cardiovascular:** Palpitation, orthostatic hypotension. **Digestive:** Gastrointestinal cramps, dry mouth, constipation, heartburn. **Musculoskeletal:** Back pain, shoulder pain, knee pain, back strain, myalgia, foot pain. **Nervous/Psychiatric:** Decreased

libido, vertigo, depression, somnolence. **Respiratory:** Common cold, nasal congestion, influenza, bronchitis, pharyngeal pain,dyspnea, pulmonary congestion, chronic sinusitis, allergic rhinitis, pharyngeal discomfort. **Skin:** Flushing, pruritus, skin inflammation, diaphoresis, cutaneous pseudolymphoma. **Special Senses:** Blurred vision, tinnitus, otalgia. **Urogenital:** Urinary tract infection.

**Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynxhas been reported (see WARNINGS).

In rare cases, intestinal angioedema has been reported in post marketing experience.

**Hypotension:** In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (1.4%), orthostatic hypotension (0.5%), other orthostatic effects (3.2%). In addition, syncope occurred in 0.8% of patients (see WARNINGS).

**Cough:** See PRECAUTIONS - Cough.

**Clinical Laboratory Test Findings:** Serum Electrolytes: (See PRECAUTIONS).
**Creatinine, Blood Urea Nitrogen:** Minor reversible increases in blood urea nitrogen and serum creatinine 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 renal artery stenosis (see PRECAUTIONS).

**Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglycerides and Calcium:** (See PRECAUTIONS).

**Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 g% and 1.5 vol%, 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.

**Liver Function Tests:** Rarely, elevations of liver enzymes and/or serum bilirubin have

occurred. (See WARNINGS, Hepatic Failure).

Other adverse reactions that have been reported with the individual components arelisted below:

**Lisinopril -** In clinical trials adverse reactions which occurred with lisinopril were also seen with lisinopril and hydrochlorothiazide. In addition, and since lisinopril has been marketed, the followingadverse reactions have been reported with lisinopril and should be considered potential adverse reactions for lisinopril and hydrochlorothiazide: **Body as a Whole:** Anaphylactoid reactions (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure), malaise, edema, facial edema, pain, pelvic pain, flank pain, chills; **Cardiovascular:** Cardiac arrest,myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension), pulmonary embolism and infarction, worsening of heart failure, arrhythmias (including tachycardia, ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia, and premature ventricular contractions), angina pectoris, transient ischemic attacks, paroxysmal nocturnal dyspnea, decreased blood pressure, peripheral edema, vasculitis; **Digestive:** Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, Hepatic Failure), gastritis, anorexia, flatulence, increased salivation; **Endocrine:** Diabetes mellitus, inappropriate antidiuretic hormone secretion; **Hematologic:** Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia, and thrombocytopenia have been reported in which a causal relationship to lisinopril cannot be excluded; **Metabolic:** Gout, weight loss, dehydration, fluid overload, weight gain; **Musculoskeletal:** Arthritis, arthralgia, neck pain, hip pain, joint pain, leg pain, arm pain, lumbago; **Nervous System/Psychiatric:** Ataxia, memory impairment, tremor, insomnia, stroke, nervousness, confusion, peripheral neuropathy (e.g., paresthesia, dysesthesia), spasm, hypersomnia, irritability; mood alterations (including depressive symptoms); hallucinations; **Respiratory:** Malignant lung neoplasms, hemoptysis, pulmonary edema, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, wheezing, orthopnea, painful respiration, epistaxis,laryngitis, sinusitis, pharyngitis, rhinitis, rhinorrhea, chest sound abnormalities; **Skin:** Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema, psoriasis, rare cases of other severe skin reactions, including toxic epidermal necrolysis and Stevens-Johnson

Syndrome (causal relationship has not been established); **Special Senses:** Visual loss, diplopia, photophobia, taste alteration,olfactory disturbance; **Urogenital:** Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, breast pain.

**Miscellaneous:** A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologicalmanifestations may occur alone or in combination with these symptoms.

**Hydrochlorothiazide - Body as a Whole:** Weakness; **Digestive:** Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice) (see WARNINGS, Hepatic Failure), pancreatitis, sialoadenitis, constipation; **Hematologic:** Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia; **Musculoskeletal:** Muscle spasm; **Nervous System/Psychiatric:** Restlessness; **Renal:** Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); **Skin:** Erythema multiforme including Stevens-Johnson Syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; **Special Senses:** Xanthopsia; **Hypersensitivity:** Purpura, photosensitivity, urticaria, necrotizing ang itis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

### Postmarketing Experience

### Non-melanoma Skin Cancer

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000mgthe risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

## OVERDOSAGE

No specific information is available on the treatment of overdosage with Lisinopril and Hydrochlorothiazide Oral Liquid. Treatment is symptomatic and supportive. Therapy with

Lisinopril and Hydrochlorothiazide Oral Liquid should be discontinued and the patient observed closely. Suggested measures include inductionof emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

**Lisinopril**

Following a single oral dose of 20 g/kg no lethality occurred in rats and death occurred in one of 20 mice receiving the same dose. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Lisinopril can be removed by hemodialysis (see WARNINGS, Anaphylactoid Reaction During Membrane Exposure).

**Hydrochlorothiazide**

Oral administration of a single oral dose of 10 g/kg to mice and rats was not lethal. 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.

## DOSAGE AND ADMINISTRATION

Lisinopril monotherapy is an effective treatment of hypertension in once-daily doses of 10 mg to 80 mg, while hydrochlorothiazide monotherapy is effective in doses of 12.5 mg per day to 50 mg per day. In clinical trials of lisinopril/hydrochlorothiazide combination therapy using lisinopril doses of 10 mg to 80 mg and hydrochlorothiazide doses of 6.25 mg to 50 mg, the antihypertensive response rates generally increased with increasing dose of either component.

The side effects (see WARNINGS) of lisinopril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of lisinopril

and hydrochlorothiazide may be associated with either or bothdose-independent or dose-dependent side effects, but addition of lisinopril in clinical trials blunted the hypokalemia normally seen with diuretics.

To minimize dose-dependent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

**Dose Titration Guided by Clinical Effect:** A patient whose blood pressure is not adequately controlled with either lisinopril or hydrochlorothiazide monotherapy may be switched to Lisinopril and Hydrochlorothiazide Oral Liquid 10 mg + 12.5 mg/5mL or Lisinopril and Hydrochlorothiazide Oral Liquid 20 mg + 12.5 mg/5mL depending on current monotherapy dose. Further increases of either or both components should depend on clinical response with blood pressure measured at the interdosing interval to ensure that there is an adequate antihypertensive effect at that time. The hydrochlorothiazide dose should generally not be increased until 2 to 3 weeks have elapsed. After addition of the diuretic it may be possible to reduce the dose of lisinopril. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen may achieve similar or greater blood-pressure control without electrolyte disturbance if they are switched to Lisinopril and Hydrochlorothiazide Oral Liquid 10 mg + 12.5 mg/5mL.

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 lisinoprilto reduce the likelihood of hypotension (see WARNINGS). If the patient's blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg of lisinopril should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and PRECAUTIONS, Drug Interactions).

Concomitant administration of Lisinopril and Hydrochlorothiazide Oral Liquid with potassium supplements, potassium salt substitutes or potassium-sparing diuretics may lead

to increases of serum potassium (see PRECAUTIONS).

**Replacement Therapy:** The combination may be substituted for the titrated individual components.

**Use in Renal Impairment:** Regimens of therapy with Lisinopril and Hydrochlorothiazide Oral Liquid need not take account of renal function as long as the patient's creatinine clearance is >30 mL/min/1.7m$^2$ (serum creatinine roughly ≤3 mg/dL or 265 µmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Lisinopril and Hydrochlorothiazide Oral Liquid is not recommended (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure).

## HOW SUPPLIED

Strength 1 - Lisinopril and Hydrochlorothiazide Oral Liquid 10 mg + 12.5 mg / 5mL

Strength 2 - Lisinopril and Hydrochlorothiazide Oral Liquid 20 mg + 12.5 mg / 5mL

Strength 3 - Lisinopril and Hydrochlorothiazide Oral Liquid 20 mg + 25 mg / 5mL

### Storage

Store at *[to be determined]*.

**Drug Name:** **Lisinopril and Hydrochlorothiazide Oral Liquid**

**Indication:** **For the treatment of hypertension, to lower blood pressure**

# REQUEST FOR WAIVER OF PEDIATRIC STUDIES

**Document Date: 29 July 2024**

Premier Research Consulting, LLC

8000 Jarvis Avenue, Suite 100
Newark, CA 94560

## TABLE OF CONTENTS

## 1 PRODUCT NAME

Lisinopril and Hydrochlorothiazide Oral Liquid

## 2 INDICATION

For the treatment of hypertension, to lower blood pressure

## 3 PEDIATRIC AGE GROUP(S) INCLUDED IN THIS REQUEST FOR WAIVER

The Petitioner requests a waiver per indication and age group as noted below.

| **Indication** | **Age Group** |
|---|---|
| | **0 to < 17 years** |
| For the treatment of hypertension, to lower blood pressure | Full Waiver* |

* The Petitioner relies on the established safety and efficacy of the Reference Listed Drug

## 4 STATUTORY REASON(S) FOR WAIVING PEDIATRIC ASSESSMENT REQUIREMENTS

The Petitioner requests a waiver as per the statutory reason noted below.

| **Statutory Reason** | **Reference of Statutory Authority** |
|---|---|
| The drug or biological product: (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients | Section 505B(a)(5)(A)(iii) of the FD&C Act<br><br>21 U.S.C. 355c(a)(5)(A)(iii) |

## 5 EVIDENCE TO SUPPORT THE STATUTORY BASIS(S) FOR THE WAIVER

The Petitioner's request meets the statutory reason for waiver as indicated above and as justified below:

1. The Lisinopril and Hydrochlorothiazide Oral Liquid product does not represent a meaningful benefit over existing treatments.
    a. Each of the components of the proposed combination (i.e., lisinopril and hydrochlorothiazide) are already approved and available individually or in combination.
    b. The proposed dosage strengths for Lisinopril and Hydrochlorothiazide Oral Liquid product are the same as that stated in the approved product labeling of the Reference Listed Drug (RLD), ZESTORETIC®, approved under NDA 019888.
    c. The active ingredients, dosage regimen, uses and route of administration (i.e., oral) of the proposed dosage strengths for Lisinopril and Hydrochlorothiazide Oral Liquid product will be the same as applicable to the RLD.
    d. The inactive ingredients in the proposed Lisinopril and Hydrochlorothiazide Oral Liquid product are not expected to impact safety, efficacy, or the pharmacokinetic profile of the active ingredients and thus, the establishment of bioequivalence to the RLD.
2. The Lisinopril and Hydrochlorothiazide Oral Liquid product is not likely to be used in a substantial number of pediatric patients.
    a. The current standard of care guidelines in both the US and Europe suggest that the treatment of pediatric hypertension should not be initiated with a fixed-dose combination product (Flynn et al., 2017; Lurbe et al., 2016).
    b. Few data exist on the use of fixed-dose combination agents in children and are fixed-dose combination agents rarely used in children (Lurbe et al., 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in & Adolescents, 2004; Stephens et al., 2012).

## 6 CERTIFICATION

The Petitioner certifies that to their best knowledge and belief, this Request for Waiver of Pediatric Studies includes all information and views on which the Request relies, and includes representative data and information known to the Petitioner which are unfavorable to the Petition.

## 7 REFERENCES

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