WORLDWIDE PRODUCT CIRCULAR

WPC-HYZ-T-042006

Tablets
HYZAAR™
(losartan potassium and hydrochlorothiazide)

MANDATORY SECTION

I. THERAPEUTIC CLASS

HYZAAR* (losartan potassium and hydrochlorothiazide) is the first combination of an angiotensin II receptor (type AT_1) antagonist and a diuretic.

II. INDICATIONS

Hypertension
HYZAAR is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy
HYZAAR is a combination of losartan (COZAAR) and hydrochlorothiazide. In patients with hypertension and left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, reduces the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see RACE).

III. DOSAGE AND ADMINISTRATION

HYZAAR may be administered with other antihypertensive agents.

HYZAAR may be administered with or without food.

Hypertension
The usual starting and maintenance dose of HYZAAR is one tablet of HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. For patients who do not respond adequately to HYZAAR 50-12.5, the dosage may be increased to one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily or two tablets of HYZAAR 50-12.5 once daily. The maximum dose is one tablet of HYZAAR 100-25 once daily or two tablets of HYZAAR 50-12.5 once daily. In general, the antihypertensive effect is attained within three weeks after initiation of therapy.

HYZAAR should not be initiated in patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics).

HYZAAR is not recommended for patients with severe renal impairment (creatinine clearance ≤30 mL/min) or for patients with hepatic impairment.

No initial dosage adjustment of HYZAAR 50-12.5 is necessary for elderly patients. HYZAAR 100-25 should not be used as initial therapy in elderly patients.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed, the dose should then be increased to losartan 100 mg and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. HYZAAR 50/12.5 and HYZAAR 100/25 are suitable alternative formulations in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

IV. CONTRAINDICATIONS

HYZAAR is contraindicated in:

- patients who are hypersensitive to any component of this product.
- patients with anuria.
- patients who are hypersensitive to other sulfonamide-derived drugs.

V. PRECAUTIONS

Losartan-Hydrochlorothiazide

Hypersensitivity: Angioedema. See SIDE EFFECTS.

Hepatic and Renal Impairment

HYZAAR is not recommended for patients with hepatic impairment or severe renal impairment (creatinine clearance ≤30 mL/min) (see DOSAGE AND ADMINISTRATION).

Losartan

Renal Function Impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan; these changes in renal function may be reversible upon discontinuation of therapy.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see DRUG INTERACTIONS).

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. 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.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

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

VI. PREGNANCY
[For Pregnancy Category, see Alternative Section XXV.]

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, HYZAAR should be discontinued as soon as possible.

Although there is no experience with the use of HYZAAR in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of the renin angiotensin system, begins in the second trimester; thus, risk to the fetus increases if HYZAAR is administered during the second or third trimesters of pregnancy.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly

other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

VII. NURSING MOTHERS

[For alternative version including animal data, see Section XXVI.]

It is not known whether losartan is excreted in human milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

VIII. PEDIATRIC USE

Safety and effectiveness in children have not been established**.**

IX. USE IN THE ELDERLY

[For alternative version including stratification by age, see Section XXVII.]

In clinical studies, there were no clinically significant differences in the efficacy and safety profiles of HYZAAR in older (≥65 years) and younger patients (<65 years).

X. RACE

[This section should be included by countries that are using the MANDATORY SECTION of the WPC verbatim or countries that do not have a CLINICAL PHARMACOLOGY section in their local Physician's Circulars; see OPTIONAL SECTION XXIe for the full description of the LIFE Study.]

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients. In the overall LIFE study population (n=9193), treatment with losartan resulted in a 13.0% risk reduction (p=0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, losartan decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan (p=0.03). In the subgroup of Black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on losartan.

XI. DRUG INTERACTIONS

[For alternative version of first paragraph, see Section XXIc.]

Losartan
In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see Hydrochlorothiazide*, Alcohol, barbiturates, or narcotics* below), ketoconazole and erythromycin. Rifampin and fluconazole have been preported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Hydrochlorothiazide
When given 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.

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 percent, respectively.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., adrenaline) - 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 - Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended. Refer to the package inserts for lithium preparations before use of such preparations.

Non-Steroidal Anti-inflammatory Drugs Including Cyclooxygenase-2 Inhibitors - In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

Drug/Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see PRECAUTIONS).

XII. SIDE EFFECTS

[For optional information including adverse experiences reported with the individual components, see Optional Section XVII.]

In clinical trials with losartan potassium–hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo.

In general, treatment with losartan potassium–hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan potassium–hydrochlorothiazide.

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, was generally well tolerated. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely with losartan.
Gastrointestinal: Hepatitis has been reported rarely in patients treated with losartan, diarrhea.
Respiratory: Cough has been reported with losartan.
Skin: Urticaria, erythroderma has been reported with losartan.

XIIa. Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of HYZAAR. Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 0.7% of patients, but in these trials, discontinuation of HYZAAR due to hyperkalemia was not necessary. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

XIII. OVERDOSAGE

[For alternative version including significant lethality, see Section XXIX.]

No specific information is available on the treatment of overdosage with HYZAAR. Treatment is symptomatic and supportive. Therapy with HYZAAR should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

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

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

XIV. AVAILABILITY

To be filled in locally.

OPTIONAL SECTION

XV. INDICATIONS

[May be substituted for Section II.]

- HYZAAR is indicated for the initial treatment of severe hypertension (SiDBP ≥110 mmHg).
- HYZAAR is also indicated for the treatment of hypertension when initial treatment with losartan or hydrochlorothiazide alone does not result in adequate control of blood pressure.

XVI. DOSAGE AND ADMINISTRATION

*May be substituted for the "***Hypertension***" paragraph in Section III.*

Hypertension

The usual starting and maintenance dose of HYZAAR is one tablet of HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. For patients who do not respond adequately to HYZAAR 50-12.5, the dosage may be increased to one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily or two tablets of HYZAAR 50-12.5 once daily. The maximum dose is one tablet of HYZAAR 100-25 once daily or two tablets of HYZAAR 50-12.5 once daily. In general, the antihypertensive effect is attained within three weeks after initiation of therapy. HYZAAR 100/12.5 (losartan 100 mg/hydrochlorothiazide 12.5 mg) is available for those patients titrated to 100 mg of COZAAR who require additional blood pressure control.

May be substituted for the "***Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy***" paragraph in Section III.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed, the dose should then be increased to losartan 100 mg and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. HYZAAR 50/12.5, HYZAAR 100/12.5 and HYZAAR 100/25 are suitable alternative formulations in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

May be added to Section III.

Severe Hypertension (SiDBP ≥110 mmHg)
The starting dose of HYZAAR for initial treatment of severe hypertension is one tablet of HYZAAR 50-12.5 once daily. For patients who do not respond adequately to HYZAAR 50-12.5 after 2 to 4 weeks of therapy, the dosage may be increased to one tablet of HYZAAR 100-25 once daily. The maximum dose is one tablet of HYZAAR 100-25 once daily.

XVII. SIDE EFFECTS

[May be added to Section XII.]

Severe Hypertension (SiDBP ≥110 mmHg)
The adverse experience profile for patients with severe hypertension (SiDBP ≥110 mmHg) treated with losartan/hydrochlorothiazide as initial therapy was similar to the adverse experience profile in patients treated with losartan monotherapy at the time of first dose, at 4 weeks of therapy, and at 6 weeks of therapy. Additionally, the adverse experience rates for hypotension, syncope, dizziness, and increased serum creatinine (all of which are signs and symptoms of hypoperfusion) did not differ between the treatment groups.

Additional side effects that have been seen with one of the individual components and may be potential side effects with HYZAAR are the following:

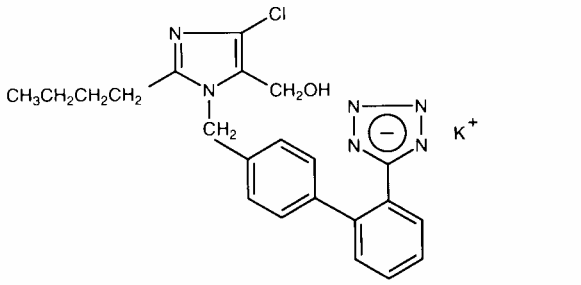
Losartan
Rash, dose-related orthostatic effects, abdominal pain, asthenia/fatigue, chest pain, edema/swelling, palpitation, tachycardia, dyspepsia, nausea, back pain, muscle cramps, headache, insomnia, cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, migraine, liver function abnormalities, anemia, myalgia, arthralgia, pruritus, dysgeusia, vomiting.

Hydrochlorothiazide
Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, paraesthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, purpura, photosensitivity, fever, necrotizing angiitis (vasculitis) (cutaneous vasculitis), respiratory distress (including pneumonitis and pulmonary edema), toxic epidermal necrolysis, hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance including hyponatremia and hypokalemia, renal dysfunction, interstitial nephritis, renal failure, muscle spasm, weakness, restlessness, transient blurred vision.

XVIII. CHEMISTRY

Losartan Potassium
Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-methanol monopotassium salt.

Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:

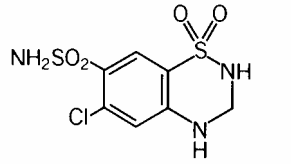


Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Hydrochlorothiazide

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



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

XIX. COMPOSITION

XIXa. Active Ingredients

HYZAAR 50-12.5 is supplied as a scored or unscored film-coated tablet containing 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide, as the active ingredients.
HYZAAR 100-12.5 is supplied as an unscored film-coated tablet containing 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide, as the active ingredients.
HYZAAR 100-25 is supplied as an unscored film-coated tablet containing 100 mg of losartan potassium and 25 mg of hydrochlorothiazide, as the active ingredients.

XIXb. Inactive Ingredients

Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose,hypromellose.

HYZAAR 50-12.5 contains 4.24 mg (0.108 mEq) of potassium. HYZAAR 100-12.5 contains 8.48 mg (0.216 mEq) of potassium. HYZAAR 100-25 contains 8.48 mg (0.216 mEq) of potassium.

HYZAAR 50-12.5, HYZAAR 100-12.5 and HYZAAR 100-25 also may contain titanium dioxide and D&C yellow No. 10 aluminum lake (quinoline yellow).

XX. STORAGE

Store at room temperature 15-30°C (59-86°F). Keep container tightly closed.

XXI. CLINICAL PHARMACOLOGY

[For an alternative brief section, see Section XXX.]

XXIa. Mechanism of Action

Losartan-Hydrochlorothiazide

The components of HYZAAR have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

Losartan
Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation. A second angiotensin II receptor has been identified as the AT_2 receptor subtype, but it plays no known role in cardiovascular homeostasis.

Losartan is a potent, synthetic, orally active compound. Based on binding and pharmacological bioassays, angiotensin II binds selectively to the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. In contrast to some peptide antagonists of angiotensin II, losartan has no agonist effects.

Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated

effects or the generation of edema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

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 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

XXIb. Pharmacokinetics

XXIb-1. Absorption

Losartan
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

XXIb-2. Distribution

Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

XXIb-3. Metabolism

Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

XXIb-4. Elimination

Losartan
Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ^{14}C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces.

Hydrochlorothiazide
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.

XXIb-5. Characteristics in Patients

Losartan-Hydrochlorothiazide
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan
The plasma concentrations of losartan and its active metabolite in elderly hypertensives are not significantly different from those in young hypertensives.

Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females. This apparent pharmacokinetic difference is not judged to be of clinical significance.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 mL/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in hemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor the active metabolite can be removed by hemodialysis.

XXIc. Drug Interactions

[Can be substituted for the first paragraph of the Mandatory DRUG INTERACTIONS, Losartan, Section XI.]

Losartan
No drug-drug pharmacokinetic interactions of clinical significance have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreases the concentrations of the active metabolite. In humans, two inhibitors of 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral losartan administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

XXId. Pharmacodynamics

Losartan
Losartan inhibits systolic and diastolic pressor responses to angiotensin II infusions. At peak, 100 mg of losartan potassium inhibits these responses by approximately 85%; 24 hours after single and multiple-dose administration, inhibition is about 26-39%.

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. During chronic (6 weeks) treatment of hypertensive patients with 100 mg/day losartan, approximately 2-3 fold increases of plasma angiotensin II were observed at time of peak plasma drug concentrations. In some patients, greater increases were observed, particularly during short term (2 weeks) treatment. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent at 2 and 6 weeks, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days. Effects of HYZAAR on PRA and angiotensin II levels were similar to those observed with 50 mg of losartan.

Since losartan is a specific antagonist of the angiotensin II receptor type AT_1, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. In a study which compared the effects of 20 mg and 100 mg of losartan potassium and an ACE inhibitor on responses to angiotensin I, angiotensin II and bradykinin, losartan was shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin. This finding is consistent with losartan's specific mechanism of action. In contrast, the ACE inhibitor was shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

Plasma concentrations of losartan and its active metabolite and the antihypertensive effect of losartan increase with increasing dose. Since losartan and its active metabolite are both angiotensin II receptor antagonists, they both contribute to the antihypertensive effect.

In a single-dose study in normal males, the administration of 100 mg of losartan potassium, under dietary high- and low-salt conditions, did not alter glomerular filtration rate, effective renal plasma flow or filtration fraction. Losartan had a natriuretic effect which was more pronounced on a low-salt diet and did not appear to be related to inhibition of early proximal reabsorption of sodium. Losartan also caused a transient increase in urinary uric acid excretion.

In nondiabetic hypertensive patients with proteinuria ($\geq$2 g/24 hours) treated for 8 weeks, the administration of losartan potassium 50 mg titrated to 100 mg significantly reduced proteinuria by 42%. Fractional excretion of albumin and IgG also was significantly reduced. In these patients, losartan maintained glomerular filtration rate and reduced filtration fraction.

In postmenopausal hypertensive women treated for 4 weeks, 50 mg of losartan potassium had no effect on renal or systemic prostaglandin levels.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL-cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

Generally losartan caused a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent with chronic therapy. In controlled clinical trials in hypertensive patients, no patients were discontinued due to increases in serum creatinine or serum potassium.

In a 12-week, parallel-design study in patients with left ventricular failure (New York Heart Association Functional Classes II-IV), most of whom were receiving diuretics and/or digitalis, losartan potassium administered in once-daily doses of 2.5, 10, 25 and 50 mg was compared to placebo. The 25-mg and 50-mg doses produced positive hemodynamic and neurohormonal effects which were maintained for the length of the study. Hemodynamic responses were characterized by an increase in cardiac index and decreases in: pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate. The occurrence of hypotension was dose related in these heart failure patients. Neurohormonal results were characterized by a reduction in circulating levels of aldosterone and norepinephrine.

XXIe. Clinical Studies

Losartan-Hydrochlorothiazide

Losartan and hydrochlorothiazide, when used in combination, are additive in their antihypertensive efficacy. The antihypertensive effect of HYZAAR is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of HYZAAR had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

In a study comparing the combination of losartan 50 mg/hydrochlorothiazide 12.5 mg with the combination captopril 50 mg/hydrochlorothiazide 25 mg in young (<65 years) and elderly (≥65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer drug-related clinical adverse experiences and discontinuations due to clinical adverse events with losartan 50 mg/hydrochlorothiazide 12.5 mg than with captopril 50 mg/hydrochlorothiazide 25 mg.

A study with 131 patients with severe hypertension showed the utility of HYZAAR administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

HYZAAR is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Severe Hypertension (Sitting Diastolic Blood Pressure [SiDBP] ≥110 mmHg)

The safety and efficacy of HYZAAR as initial therapy for severe hypertension (baseline mean SiDBP ≥110 mmHg confirmed on 2 separate occasions) was demonstrated in a six-week double-blind, randomized, multicenter study of 585 patients with severe hypertension. The primary endpoint was a comparison at 4 weeks of patients who achieved goal diastolic blood pressure (trough SiDBP <90 mmHg) on losartan/hydrochlorothiazide 50/12.5 mg versus patients on losartan 50 mg titrated to 100 mg as needed to reach goal diastolic blood

pressure. The secondary endpoint was a comparison at 6 weeks of patients who achieved goal diastolic blood pressure on losartan/hydrochlorothiazide 50/12.5 mg titrated as needed to losartan/hydrochlorothiazide 100/25 mg versus patients on losartan 50 mg titrated to 100 mg and then to 150 mg. In a post-hoc analysis, patients who achieved goal systolic blood pressure (trough SiSBP <140 mmHg) were compared for the 2 treatment groups at 4 and 6 weeks.

After 4 weeks of therapy, more patients who received losartan/hydrochlorothiazide 50/12.5 mg combination therapy reached target diastolic blood pressure than those who received losartan 50 or 100 mg monotherapy (17.6% versus 9.4%, respectively; p=0.007). Similarly, after 6 weeks of therapy, more patients who received the combination regimen reached target diastolic blood pressure than those who received the monotherapy regimen (29.8% versus 12.5%, respectively; p<0.001). Additionally, more patients achieved goal systolic blood pressure on combination therapy versus monotherapy at each time point (week 4: 24.5% versus 11.9%, respectively, p<0.001; week 6: 36.9% versus 14.1%, respectively, p<0.001). The safety and tolerability of losartan/hydrochlorothiazide for patients with severe hypertension were comparable to losartan monotherapy at the time of first dose, at 4 weeks of therapy, and at 6 weeks of therapy.

Losartan

The antihypertensive efficacy of losartan was demonstrated in 11 controlled studies involving 1679 patients on losartan, 471 patients on placebo and 488 patients receiving a variety of comparator agents. Once-daily administration of losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; in clinical studies of up to one year the antihypertensive effect was maintained. Measurement of blood pressure at trough (24 hours postdose) relative to peak (5-6 hours postdose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours postdose. The maximal antihypertensive effect was attained 3-6 weeks after initiation of therapy. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure.

The administration of losartan 50-100 mg once daily produced a significantly greater antihypertensive effect than captopril 50-100 mg given once daily. The antihypertensive effect of once-daily administration of losartan 50 mg was shown to be similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of losartan 50-100 mg was shown to be comparable to once-daily administration of atenolol 50-100 mg. The effect of administration of losartan 50-100 mg once daily also was equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy.

Losartan is equally effective in males and females and in younger (<65 years) and older (≥65 years) hypertensives. Although losartan was antihypertensive in all races studied, as with other drugs that affect the renin-angiotensin system, black hypertensive patients had a smaller average response to losartan monotherapy than non-black patients.

When given together with thiazide-type diuretics, the blood pressure lowering effects of losartan are approximately additive.

Because losartan selectively blocks the AII receptor site, it is expected that patients taking losartan will not develop cough. In an 8-week controlled study of the incidence of cough in hypertensive patients with a history of cough during ACE inhibitor therapy, the incidence of cough reported by patients receiving losartan or an agent not associated with ACE inhibitor-induced cough (hydrochlorothiazide) was similar and was significantly less than in patients rechallenged with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

LIFE Study: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomized, triple-blind, active-controlled study of 9193 hypertensive patients aged 55 to 80 years (mean 67 years) with ECG-documented left ventricular hypertrophy. Of the patients enrolled at baseline, 1195 (13%) had diabetes; 1326 (14%), isolated systolic hypertension; 1468 (17%), coronary heart disease; and 728 (8%), cerebrovascular disease. The goal of the study was to demonstrate the cardiovascular protective effects of losartan versus atenolol, over and above the benefits of blood pressure control alone (blood pressure was measured at trough). To meet this objective, the study was designed to achieve equal blood pressure in both treatment groups. Patients were randomized to receive once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure. In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms, respectively).

In both treatment groups, blood pressure was significantly lowered to similar levels and a similar proportion of patients achieved goal blood pressure. The mean length of follow-up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke, and myocardial infarction. The results showed that treatment with losartan resulted in a 13.0% risk reduction (p=0.021) as compared with atenolol for patients reaching the primary composite endpoint.

Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups. The effect of losartan on the primary composite endpoint appeared to be over and above its beneficial effects on blood pressure control alone.

For the primary composite endpoint, in the subgroups of patients with a baseline history of diabetes mellitus (n=1195) or isolated systolic hypertension (ISH) (n=1326), the results of treatment with losartan were consistent with the benefit of therapy with losartan seen in the overall study population: in diabetic patients, a 24% risk reduction (p=0.03) was observed

and in patients with ISH, a 25% risk reduction (p=0.06) was observed. Consistent with the results seen in the overall population, a reduction in stroke was an important contributor to the benefit observed in patients with diabetes or ISH.

For hypertensive patients with left ventricular hypertrophy, HYZAAR is a suitable alternative formulation in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide once daily for the reduction of cardiovascular morbidity and mortality.

Race: In the LIFE study, Black patients treated with atenolol (n=263) were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan (n=270). Based on the LIFE study, the benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy.

In this study, losartan was generally well tolerated, and the tolerability profile of losartan was superior to atenolol as evidenced by a significantly lower incidence of discontinuations due to side effects.

XXII. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that HYZAAR affects the ability to drive and use machines.

XXIII. INFORMATION FOR PATIENTS

[For inclusion in Physicians Circulars only. Not to be substituted for a Patient Package Insert.]

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

XXIV. ANIMAL TOXICOLOGY

XXIVa. Acute Toxicity

Losartan

The oral LD_{50} of losartan potassium in male mice is 2248 mg/kg (6744 mg/m^2) (1124 times the maximum recommended human daily dose). Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m^2) and 2000 mg/kg (11,800 mg/m^2) (500 and 1000 times** the maximum recommended daily human dose), respectively.

Hydrochlorothiazide

The oral LD_{50} of hydrochlorothiazide is greater than 10,000 mg/kg in both mice and rats.

XXIVb. Chronic Toxicity

** Based on a patient weight of 50 kg.

Losartan-Hydrochlorothiazide
The toxic potential of losartan potassium-hydrochlorothiazide was evaluated in repeated dose oral toxicity studies for up to six months in rats and dogs. There were no findings that would preclude administration to man at the therapeutic dosage level.

XXIVc. Carcinogenesis

Losartan
Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

Hydrochlorothiazide
Two-year feeding studies in mice and rats 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). The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice.

XXIVd. Mutagenesis

Losartan-Hydrochlorothiazide
Losartan potassium-hydrochlorothiazide was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and i*n vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan
Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that were approximately 1700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m^2) (750 times the maximum recommended daily human dose). In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Hydrochlorothiazide
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 to 1300 μg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

XXIVe. Reproduction

Losartan-Hydrochlorothiazide

Losartan potassium-hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day of losartan in combination with 33.75 mg/kg/day of hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and hydrochlorothiazide that were approximately 260-, 120-, and 50-fold greater than those achieved in man with 50 mg of losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, the coadministration of losartan potassium/hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

Losartan

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Hydrochlorothiazide

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 and 4 mg/kg, respectively, prior to conception and throughout gestation.

XXIVf. Development

Losartan-Hydrochlorothiazide

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium-hydrochlorothiazide. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F_1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including decreased body weight and renal toxicity, also occurred when pregnant rats were treated with losartan potassium-hydrochlorothiazide during late gestation and/or lactation.

Losartan

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

Hydrochlorothiazide

Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the maximum 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 4-5.6 mg/kg/day (approximately 2-3 times the maximum recommended human dose) did not impair fertility or produce birth abnormalities in the offspring.

ALTERNATIVE SECTION

XXV. PREGNANCY

[Can be added to Section VI.]

Pregnancy Categories C (first trimester) and D (second and third trimester).

XXVI. NURSING MOTHERS

[Includes animal data. Can be substituted for Section VII.]

It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

XXVII. USE IN THE ELDERLY

[Includes stratification by age. Can be substituted for Section IX.]

Of the total number of patients in controlled clinical studies of hypertension with HYZAAR, 206 patients (19%) were 65 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

XXVIII. ADVERSE REACTIONS

[May be included with Mandatory Section XII.]

In double-blind controlled clinical trials, the following adverse experiences reported with HYZAAR occurred in ≥1 percent of patients, regardless of drug relationship:

	Losartan Potassium – Hydrochlorothiazide	Placebo
	(n=1088)	(n=187)
Body as a Whole		
Abdominal pain	1.3	1.1
Asthenia/fatigue	3.1	3.7
Edema/swelling	1.2	1.6
Cardiovascular		
Palpitation	1.6	0.0
Digestive		
Diarrhea	1.6	2.1
Nausea	1.5	2.1
Musculoskeletal		
Back pain	2.9	0.5
Nervous/Psychiatric		
Dizziness	5.8	3.2
Headache	8.0	15.0
Respiratory		
Bronchitis	1.1	1.6
Cough	2.2	2.1
Pharyngitis	1.2	1.6
Sinusitis	1.0	0.5
Influenza	1.2	0.5
Upper respiratory infection	5.8	4.8
Skin		
Rash	1.3	0.5

XXIX. OVERDOSAGE

[Includes significant lethality. May be substituted for Section XIII.]

Losartan

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m^2) and 2000 mg/kg (11,800 mg/m^2), respectively.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The oral LD_{50} of hydrochlorothiazide is greater than 10,000 mg/kg in both mice and rats.

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.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

XXX. CLINICAL PHARMACOLOGY - Brief Version

[Can be substituted for Section XXI.]

Pharmacodynamic properties

Losartan-Hydrochlorothiazide
The components of HYZAAR have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

Losartan and hydrochlorothiazide, when used in combination are additive in their antihypertensive efficacy.

The antihypertensive effect of HYZAAR is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of HYZAAR had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

In a study comparing the combination of losartan 50 mg/hydrochlorothiazide 12.5 mg with the combination captopril 50 mg/hydrochlorothiazide 25 mg in young (<65 years) and elderly (≥65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer drug-related clinical adverse experiences and discontinuations due to clinical adverse events with losartan 50 mg/hydrochlorothiazide 12.5 mg than with captopril 50 mg/hydrochlorothiazide 25 mg.

A study with 131 patients with severe hypertension showed the utility of HYZAAR administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

HYZAAR is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Losartan

Losartan is an oral angiotensin II receptor (type AT_1) antagonist. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation. Based on binding and pharmacological bioassays, angiotensin II binds selectively to the AT_1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade.

Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of edema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with losartan's specific mechanism of action. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

In patients with left ventricular failure, 25-mg and 50-mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

In clinical studies, once-daily administration of losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; in clinical studies of up to one year the antihypertensive effect was maintained. Measurement of blood pressure at trough (24 hours postdose) relative to peak (5-6 hours postdose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours postdose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

The administration of losartan 50-100 mg once daily produces a significantly greater antihypertensive effect than captopril 50-100 mg given once daily. The antihypertensive effect of losartan 50 mg is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of losartan 50-100 mg is comparable to once-daily administration of atenolol 50-100 mg. The effect of administration of losartan 50-100 mg once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy.

Losartan is equally effective in males and females and in younger (<65 years) and older (≥65 years) hypertensives. Although losartan is antihypertensive in all races, as with other drugs that affect the renin-angiotensin system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

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 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetic properties

Absorption

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan
Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
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.

Characteristics in Patients

Losartan-Hydrochlorothiazide
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by hemodialysis.