

Prescribing Information

For the use of Registered Medical
Practitioner, Hospital or a Laboratory Only.

**COMPOSITION:**

Each film coated tablet contains:
Losartan Potassium USP 50 mg.

DESCRIPTION:

White colored, oblong shaped, film coated tablets having a break line on one side. **ZYLtan** (Losartan potassium) is an angiotensin II receptor (type AT₁) antagonist.

CLINICAL PHARMACOLOGY:**Mechanism of Action**

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both Losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than Losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Neither Losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacodynamics and Clinical Effects**Adult Hypertension**

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following Losartan administration. In spite of the effect of Losartan on aldosterone secretion, very little effect on serum potassium was observed.

Losartan has no effects on glomerular filtration rate, renal plasma flow or filtration fraction. There are no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dL) during chronic oral administration.

The effect of Losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of Losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of Losartan. There was essentially no change in average heart rate in Losartan-treated patients in controlled trials.

Pharmacokinetics**General**

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows Losartan treatment. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled Losartan potassium, circulating plasma radioactivity is primarily attributed to Losartan and its active metabolite. In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of Losartan to its metabolites. Minimal conversion of Losartan to the active metabolite (less than 1% of the dose compared to

14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The terminal half-life of Losartan is about 2 hours and of the metabolite is about 6-9 hours.

The pharmacokinetics of Losartan and its active metabolite are linear with oral Losartan doses up to 200 mg and do not change over time. Neither Losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, Losartan is well absorbed (based on absorption of radiolabeled Losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of Losartan is approximately 33%. About 14% of an orally-administered dose of Losartan is converted to the active metabolite. Mean peak concentrations of Losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of Losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of Losartan. A meal slows absorption of Losartan and decreases its C_{max} but has only minor effects on Losartan AUC or on the AUC of the metabolite (about 10% decreased).

The pharmacokinetics of Losartan and its active metabolite were also determined after IV doses of each component separately in healthy volunteers. The volume of distribution of Losartan and the active metabolite is about 34 liters and 12 liters, respectively. Total plasma clearance of Losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. After single doses of Losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of Losartan and its metabolites. Following oral ¹⁴C-labeled Losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled Losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Both Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that Losartan crosses the blood-brain barrier poorly, if at all.

Special Populations

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of Losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of Losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary.

Renal Insufficiency: Following oral administration, plasma concentrations and AUCs of Losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both Losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither Losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted.

Hepatic Insufficiency: 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-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of Losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment.

INDICATIONS:**Hypertension**

ZYLtan is indicated for the treatment of hypertension.

Hypertensive Patients with Left Ventricular Hypertrophy

ZYLtan is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients.

Nephropathy in Type 2 Diabetic Patients

ZYLtan is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥ 300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, Losartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation).

DOSAGE AND ADMINISTRATION:**Adult Hypertensive Patients**

ZYLtan may be administered with other antihypertensive agents, and with or without food.

Dosing must be individualized. The usual starting dose of **ZYLtan** is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) and patients with a history of hepatic impairment. **ZYLtan** can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of Losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks.

If blood pressure is not controlled by **ZYLtan** alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect.

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of **ZYLtan** once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of **ZYLtan** should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response.

Nephropathy in Type 2 Diabetic Patients

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response.

ZYLtan may be administered with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

CONTRAINDICATIONS:

ZYLtan is contraindicated in patients who are hypersensitive to any component of this product.

Concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m²).

WARNING AND PRECAUTIONS:**Warnings:****Fetal/Neonatal Morbidity and Mortality**

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, **ZYLtan** should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of **ZYLtan** as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, **ZYLtan** should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or

dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m² basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of Losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension Volume-Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with **ZYLTAN**. These conditions should be corrected prior to administration of **ZYLTAN**, or a lower starting dose should be used.

PRECAUTIONS:

General

Hypersensitivity: Angioedema.

Impaired Hepatic Function

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of Losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with **ZYLTAN**; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with **ZYLTAN**.

Increases in serum creatinine or blood urea nitrogen (BUN) have been reported. Similar effects have been reported with **ZYLTAN**; in some patients, these effects were reversible upon discontinuation of therapy.

Electrolyte Imbalance

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated with **ZYLTAN**.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the in vitro alkaline elution and in vitro and in vivo chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, in vitro alkaline elution, and in vitro chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of Losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p < 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section.

Nursing Mother

It is not known whether Losartan is excreted in human milk, but significant levels of Losartan and its active metabolite were shown to be present in rat 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.

Geriatric Use

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.

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.

Potassium Supplements

A patient receiving **ZYLTAN** should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

DRUG INTERACTIONS:

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of Losartan and its active metabolite. In humans, two inhibitors of P450 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 administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased Losartan 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.

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.

Lithium

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 Agents including Selective Cyclooxygenase-2 Inhibitors

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

Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of angiotensin II receptor antagonists, including Losartan. This interaction should be given consideration in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with angiotensin II receptor antagonists.

ACE inhibitors

The use of losartan with an ACE inhibitor may increase the risk of hyperkalemia, hypotension, and syncope, particularly in patients with atherosclerotic disease or heart failure, or in diabetics who have end-organ damage. Such combinations should be reserved for selected cases with close monitoring of renal function.

ADVERSE EFFECTS:

The adverse experiences reported in $\geq 1\%$ of patients treated with Losartan and more commonly than placebo are: Musculoskeletal: muscle cramps, back pain, leg pain; Nervous System/Psychiatric: Dizziness; Respiratory: nasal congestion; Upper respiratory infections: Sinusitis

The following adverse events were also reported at a rate of 1% or greater in patients treated with Losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis, diarrhea, dyspepsia, myalgia, insomnia, cough, sinus disorder.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to Losartan or other adverse events that occurred in $< 1\%$ of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to Losartan: Body as a Whole: facial edema, fever, orthostatic effects, syncope; Cardiovascular: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; Digestive: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; Hematologic: anemia; Metabolic: gout; Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; Respiratory: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; Skin: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria;

Special Senses: blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; Urogenital: impotence, nocturia, urinary frequency, urinary tract infection.

Cases of cough, including positive re-challenges, have been reported.

The following additional adverse reactions have been reported:

Digestive: Hepatitis.

General Disorders and Administration Site Conditions: Malaise.

Hemic: Thrombocytopenia.

Hypersensitivity: 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-Schönlein purpura, has been reported. Anaphylactic reactions have been reported.

Metabolic and Nutrition: Hyperkalemia, hyponatremia have been reported with Losartan.

Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Nervous system disorders: Dysgeusia

Respiratory: Dry cough (see above).

Skin: Erythroderma

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of **ZYLTAN**.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with **ZYLTAN** alone.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with **ZYLTAN** alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with **ZYLTAN** alone, one patient ($< 0.1\%$) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE:

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdose in humans. The most likely manifestation of overdose 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.

STORAGE:

Store below 30°C, protected from light.

SHELF LIFE:

36 Months

PRESENTATION:

Available in a pack of 10 X 10's tablets or 3 X 10's tablets.

DATE OF REVISION:

13/03/2025

Product Registration Holder:

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