LORTAN Tablet
(losartan potassium)

USE IN PREGNANCY

Drugs that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus. When pregnancy is detected, discontinue LORTAN as soon as possible.

I. THERAPEUTIC CLASS

LORTAN (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT_1) antagonist. LORTAN also provides a reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy and renal protection for type 2 diabetic patients with proteinuria.

II. INDICATIONS

Hypertension

LORTAN is indicated for the treatment of hypertension.

Hypertensive Patients with Left Ventricular Hypertrophy

LORTAN is indicated for the reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy (see RACE).

Renal Protection in Type 2 Diabetic Patients with Proteinuria

LORTAN is indicated to delay the progression of renal disease as measured by a reduction in the incidence of doubling of serum creatinine and end stage renal disease (need for dialysis or renal transplantation), and to reduce proteinuria.

III. DOSAGE AND ADMINISTRATION

LORTAN may be administered with or without food.

LORTAN may be administered with other antihypertensive agents.

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see PRECAUTIONS).

No initial dosage adjustment is necessary for elderly patients up to 75 years of age, or for patients with mild renal impairment. For patients above 75 years of age, patients with moderate to severe renal impairment and patients on dialysis, a lower starting dose of 25 mg is recommended. A lower dose should be considered for patients with a history of hepatic impairment (see PRECAUTIONS).

Reduction in the Risk of Stroke in Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of LORTAN once daily. A low dose of hydrochlorothiazide should be added and/or the dose of LORTAN should be increased to 100 mg once daily based on blood pressure response.

Renal Protection in Type 2 Diabetic Patients with Proteinuria

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. LORTAN may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

IV. CONTRAINDICATIONS

LORTAN is contraindicated in patients who are hypersensitive to any component of this product.
The concomitant use of LORTAN with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73m^2) (see DRUG INTERACTIONS).

V. PRECAUTIONS

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue LORTAN as soon as possible. See PREGNANCY.

Hypersensitivity: Angioedema. See SIDE EFFECTS.

Hypotension and Electrolyte/Fluid Imbalance

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of LORTAN, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

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 LORTAN as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see SIDE EFFECTS and *Laboratory Test Findings*).

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia (see DRUG INTERACTIONS).

Liver Function Impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

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 LORTAN; these changes in renal function may be reversible upon discontinuation of therapy.

No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 mL/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 mL/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see DRUG INTERACTIONS).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

VI. PREGNANCY

Although there is no experience with the use of LORTAN 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 LORTAN is administered during the second or third trimesters of pregnancy.

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue LORTAN as soon as possible.

These adverse outcomes are usually associated with the use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

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

VII. NURSING MOTHERS

It is not known whether losartan is excreted in human milk. Because many drugs are excreted in human milk and 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.

Neonates with a history of *in utero* exposure to LORTAN:
If oliguria or hypotension occur, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

IX. USE IN THE ELDERLY

In clinical studies there was no age-related difference in the efficacy or safety profile of losartan.
Presently there is limited clinical experience in patients above 75 years of age; a lower starting dose of 25 mg once daily is recommended.

X. RACE

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of LORTAN 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 LORTAN 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, LORTAN 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 LORTAN (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 LORTAN.

XI. DRUG INTERACTIONS

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole, and erythromycin. Rifampin and fluconazole have been reported 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, salt substitutes containing potassium, or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) 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 (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on LORTAN and other agents that affect the RAAS (see CONTRAINDICATIONS and PRECAUTIONS).

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of LORTAN which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking LORTAN.

XII. SIDE EFFECTS

LORTAN has been found to be generally well tolerated in controlled clinical trials for hypertension; side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with LORTAN was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with LORTAN. In addition, dose-related orthostatic effects were seen in less than one percent of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.

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

	LORTAN (n=2085)	Placebo (n=535)
Body as a Whole		
Abdominal pain	1.7	1.7
Asthenia/fatigue	3.8	3.9
Chest pain	1.1	2.6
Edema/swelling	1.7	1.9
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

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

In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with LORTAN as compared to atenolol (242 patients versus 320 patients, respectively,

p<0.001). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of LORTAN or an adverse effect of atenolol.

LORTAN was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance).

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.
Gastrointestinal: Hepatitis (reported rarely), liver function abnormalities, vomiting.
General disorders and administration site conditions: Malaise.
Hematologic: Anemia, thrombocytopenia (reported rarely).
Musculoskeletal: Myalgia, arthralgia.
Nervous System/Psychiatric: Migraine, dysgeusia.
Reproductive system and breast disorders: Erectile dysfunction/impotence.
Respiratory: Cough.
Skin: Urticaria, pruritus, erythroderma, photosensitivity.

XIIa. Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of LORTAN. Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients in the hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with proteinuria, 9.9% of patients treated with LORTAN and 3.4% of patients treated with placebo developed hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance). Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

XIII. OVERDOSAGE

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.

XIV. AVAILABILITY

LORTAN is available in packs of 30’s and 90's as 50 mg and 100 mg.

XV. STORAGE CONDITIONS

Store below 30°C.

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