Losartan potassium (Cozaar™)

Classification:

Nonpeptide angiotensin II receptor blocker (ARB)[1,2,3]

Pharmacology[1,2,3]

Losartan works through the Renin-angiotensin-aldosterone pathway (RAAS). It blocks the binding of angiotensin II, which is formed from angiotensin I via ACE enzyme and is a potent vasoconstrictor. Angiotensin II also stimulates the secretion of aldosterone by the adrenal cortex. Losartan and its active metabolite(s) inhibit the vasoconstrictor and aldosterone-secreting effects of angiotensin II selectively via AT1 receptor which is located in several tissues.

Indications[1,2,3]

FDA-labeled indications include:

Hypertension - adults and children > 6 years of age

Diabetic nephropathy in T2DM with an elevated SCr and proteinuria (urinary albumin to creatinine ratio > 300 mg/g)

Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy

Pharmacokinetics[1,2,3]

Absorption	Tmax:1 hour Bioavailability: 33% Food effects: slows absorption; decreases Cmax, but only has minor effects on the AUC Carboxylic acid (active metabolite), Tmax, oral: 3-4 hours
Distribution	Highly protein bound (98.7%) in human plasma. Volume of distribution (Vd): 34 L Carboxylic acid (active metabolite), protein binding: 99.8% Carboxylic acid (active metabolite) Vd: 12 L
Metabolism	Hepatic: extensive first-pass metabolism via CYP2C9 and 3A4 Carboxylic acid metabolite: active Substrate of CYP2C9; possible substrate of CYP3A4
Excretion	Renal clearance: 75 ml/min Renal excretion: 35% (4% unchanged, 6% as active metabolite) Fecal excretion: 60% Total body clearance: 600 ml/min Dialyzable: no (hemodialysis); no (peritoneal dialysis)

Dosage/Administration[1,2,3]

Adult hypertensive patients

Dosing individualized; standard starting dose is 50 mg once daily, with 25 mg once daily dose used in those with possible depletion of intravascular volume (including patients treated with diuretics) and those with a history of liver impairment. Dosing range is 25-100 mg per day in 1 or 2 divided daily doses.

Pediatric hypertensive patients > 6 years old

Recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) given as a tablet or a suspension. Dose adjustments made according to patient blood pressure response. Doses over 1.4 mg/kg/day (or above 100 mg/day) have not been studied in pediatric patients.

Diabetic nephropathy in T2DM

Dosing individualized; standard starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on patient blood pressure response.

Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy

Recommended starting dose is 50 mg once daily. May increase to 100 mg once daily based on patient blood pressure response. May use in combination with a thiazide diuretic.

Use in Special Population[1,2,3]

Adults

Renal impairment: no adjustment needed

Renal impairment, volume depleted patients: start at 25 mg once daily; adjust according to blood pressure response; a 25 mg dose given BID may be needed

Liver impairment (mild-moderate): start at 25 mg once daily

Hemodialysis: no adjustment needed

Pediatric

Renal impairment (eGFR < 30 ml/min): use not recommended

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause injury or death to the developing fetus. Discontinue as soon as possible if pregnancy is suspected. Pregnancy category D.

Lactation

Significant levels of losartan and its active metabolite were shown to be present in rat milk, however there are no studies showing whether losartan in excreted in human milk. Therefore, a decision should be made whether to discontinue nursing or discontinue the medication since there is a potential for adverse effects to the nursing infant.

Contraindication[1,2,3]

Losartan is contraindicated in those who are hypersensitive to any component of this agent.

Allergic cross-reactivity for ARBs is not well-established, however the possibility cannot be ruled out due to similarities in chemical structure and/or pharmacologic actions.

Do not take losartan along with aliskiren in patients with diabetes. Losartan decreases the effects of aliskiren.

Precautions[2]

Losartan Potassium can cause hypotension, that is sometimes symptomatic, in volume-depleted or salt-depleted patients which can include those being treated with diuretic therapy.

Avoid use of losartan with other renin-angiotensin system inhibitors.

Hyperkalemia has also been reported with use of losartan. Concomitant use with other drugs that may increase serum potassium may lead to the hyperkalemia. Monitoring is recommended. Dose reduction or interruption may also be necessary if hyperkalemia occurs.

Renal function deterioration, including acute renal failure, may occur. There is an increased risk with chronic kidney disease, renal artery stenosis, severe congestive heart failure, or volume depletion. Withholding or discontinuation of losartan may be necessary.

Adverse Effects[3]

In controlled clinical trials, discontinuation due to adverse events occurred in 2.3% of patients receiving losartan compared to 3.7% of patients receiving placebo.

In 4 clinical trials of losartan for hypertension involving over 1000 patients, the adverse events that occurred in $\geq$ 2% of patients treated with losartan and more commonly than placebo were: dizziness (3% vs. 2%), upper respiratory infection (8% vs. 7%), nasal congestion (2% vs. 1%), and back pain (2% vs. 1%).

Less common adverse events reported include: anemia, depression, somnolence, headache, sleep disorders, paresthesia, migraine, vertigo, tinnitus, palpitation, syncope, atrial fibrillation, CVA, dyspnea, abdominal pain, constipation, nausea, vomiting, urticaria, pruritis, rash, photosensitivity, myalgia, arthralgia, impotence, and edema.

During post-marketing the following side effects were reported: Hepatitis, malaise, thrombocytopenia, angioedema, hypersensitivity, hyperkalemia, hyponatremia, rhabdomyolysis, dysgeusia, dry cough, and erythoderma.

Persistent cough associated with ACE-inhibitor use is often a cause for discontinuation. Two studies of hypertension patients who experienced cough while receiving an ACE-inhibitor were randomized to losartan, lisinopril, placebo, or hydrochlorothiazide. The authors found that, in a population that had cough associated with ACE-inhibitor therapy, the incidence of cough with losartan is similar to hydrochlorothiazide or placebo.

Monitoring[2]

Evaluate blood pressure response until control is achieved in patients initiating or adjusting antihypertensive medication.

Monitor renal function periodically in patients whose kidney function may depend on the activity of the renin-angiotensin system (e.g., renal artery stenosis, chronic kidney disease, severe congestive heart failure, volume depletion) or in patients receiving concomitant NSAIDs.

Monitor serum potassium periodically during treatment, especially when used concomitantly with drugs that may raise potassium levels.

Monitor electrolytes in patients receiving concomitant agents that affect the renin-angiotensin system.

In patients initiating antihypertensive therapy, monitoring the following at baseline and as clinically indicated: fasting blood glucose, serum creatinine, electrolytes, urinalysis, lipid profile, and CBC.

Electrolytes and renal function should be assessed 2-4 weeks after initiating losartan. Serum sodium and potassium should be monitored during dose titration.

Interactions[1,2,3]

Losartan has the following clinically important drug interactions:

Aliskiren

- Concomitant use of aliskiren with losartan is contraindicated.

Agents increasing serum potassium

- Coadministration of losartan with other drugs that may raise serum potassium levels may result in hyperkalemia

ACE-inhibitors

- Concomitant use of an ACE-inhibitor along with losartan is not recommended.
- Dual blockade of RAAS system increases risk of hypotension, hyperkalemia, and renal impairment. Either can increase toxicity of the other and should not be used together.

Cimetidine

- Administration of losartan in conjunction with cimetidine led to a 18% increase in AUC of losartan, but it did not affect the PK of its active metabolite.

Phenobarbital

- Administration of losartan in conjunction with phenobarbital led to a 20% reduction in the AUC of losartan and its active metabolite.

Rifampin

- Administration of losartan in conjunction with rifampin led to an AUC reduction [40% AUC reduction in the active metabolite; 30% AUC reduction in losartan].

Fluconazole

- Administration of losartan in conjunction with fluconazole decreased the AUC of the active metabolite by 40%, but it increased the AUC of losartan by 70% following multiple doses.

Lithium

- Lithium excretion may be reduced if coadministered with losartan.
- Serum lithium levels should be monitored closely if lithium salts are to be co-administered with ARBs.

NSAIDs (including COX-2 inhibitors)

- In those who are elderly, volume depleted (on diuretic therapy), or with poor renal function, use of losartan with NSAIDs may result in deterioration of kidney function, including possible acute renal failure. These effects are usually reversible.

Efficacy

Four studies of losartan as monotherapy were completed to study the efficacy for hypertension. In these studies, 1075 patients were randomized to several doses of losartan and 334 to placebo. Doses of 50, 100, and 150 mg once daily gave statistically significant systolic and diastolic mean decreases in blood pressure compared to placebo. The dose of 150mg did not have a greater effect than the 50 or 100mg doses. A larger trough was found in response to twice daily doses of 50 and 100mg doses compared to the once daily dosing. Men, women, patients under 65, and patients over 65 had similar responses. Losartan was effective in blood pressure reduction regardless of race, but the effect was less in African American patients (usually a low-renin population).[3]

The 2017 ACC/AHA Hypertension guidelines recommend thiazide diuretics, calcium-channel blockers (CCBs), ACE inhibitors, or ARBs as first line therapy. Patient factors such as race and comorbid conditions should be considered when choosing a specific class. For African American patients, ARBs may be better tolerated than ACE inhibitors, with less cough and angioedema, but there is currently no proven advantage over ACE inhibitors in preventing stroke or CVD in this population. These guidelines also recommend that patients with chronic cough, a history of ACE inhibitor-induced cough, or bronchial responsiveness while on an ACE inhibitor should use an ARB instead.[4]

The LIFE study compared losartan and atenolol in hypertensive patients with ECG-documented left ventricular hypertrophy. Patients received losartan 50 mg or atenolol 50 mg. If goal blood pressure was not met, hydrochlorothiazide was added first, followed by an increase in dose of losartan or atenolol to 100 mg. Other antihypertensives were added for blood pressure control after these initial steps if needed. The primary endpoint was first occurrence of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Treatment with losartan resulted in a 13% reduction in risk of primary endpoint compared to the atenolol group. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol.[3]

In the RENAAL study, patients with type 2 diabetes with nephropathy were randomized to losartan 50 mg once daily or placebo. The drug was titrated to 100 mg if blood pressure was not achieved. The primary endpoint was the time to first occurrence of any of the following events: doubling of serum creatinine, end-stage renal disease, or death. Treatment with losartan resulted in a 16% risk reduction in this primary composite endpoint.[3]

Dosage Forms/Cost

Drug	Dose	Price/tablet	Price/month (30 tablets)
Losartan	25 mg	$0.35	$10.50
Losartan	50 mg	$0.25	$7.50
Lisinopril	10 mg	$0.07	$2.10
Lisinopril	20 mg	$0.08	$2.40

Special Considerations

Boxed Warning[2]

- **Discontinue losartan as soon as possible when pregnancy is detected. Fetal injury or death can be caused by drugs that act directly on the renin angiotensin system.**

Summary/Conclusion

Losartan is FDA approved for hypertension, diabetic nephropathy in type 2 diabetes mellitus with an elevated SCr and proteinuria, and reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy. It has been studied in many different trials, has a favorable side effect profile, and is a first-line therapy option for hypertension. In addition, it is available as a generic and is comparable in cost to the example ACE-inhibitor, lisinopril.

Recommendation

It is recommended to add losartan to the drug formulary on regular status due to its efficacy for a number of indications and its place in the hypertension guidelines. Generic losartan is also comparable in cost to the example ACE-inhibitor, lisinopril. Manufacturers are currently producing impurity-free losartan, however, due to past recalls, it is recommended that literature and FDA updates be monitored on a periodic basis for additional recall status information.

References

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