For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory xxxxxxxx-8883

TOZAAR

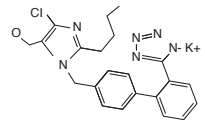
(Losartan Potassium Tablets, 25mg and 50mg)

COMPOSITION

Tozaar 25: Each film coated tablet contains Losartan potassium U.S.P. 25mg
Tozaar 50: Each film coated tablet contains Losartan potassium U.S.P. 50mg

PROPERTIES

Losartan potassium represents the first of a new class of orally active agents- the non-peptide angiotensin-II receptor (type AT1) antagonist indicated for the treatment of hypertension. Chemically it is 2-Butyl-4-chloro-5-(hydroxymethyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl] imidazole potassium salt. It is white to light yellow crystalline powder soluble in water, methanol and ethanol and insoluble in chloroform. Its empirical formula is $C_{22}H_{22}ClKN_6O$ and molecular weight is 461. The structure of Losartan potassium is



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Losartan potassium represents the first of a new class of antihypertensives, is a specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II is a potent vasoconstrictor and the primary active hormone of the renin-angiotensin-aldosterone system, playing a major part in the pathophysiology of hypertension. The cardiovascular homeostatic effects of angiotensin II are elicited through the AT1 receptor.

Losartan is a potent, synthetic orally active compound, which binds selectively to the AT1 receptor. In vitro and In vivo, both Losartan and its pharmacologically active metabolite, E-3174 block all physiologically relevant actions of angiotensin II including vasoconstriction, sodium and water retention and sympathetic stimulation. This leads to reduction in the blood pressure. Losartan does not have agonist effects and does not bind or block other hormone receptors or ion channels important in cardiovascular regulation.

PHARMACOKINETICS

Following oral administration, Losartan is well absorbed and undergoes substantial first-pass metabolism; the systemic bioavailability is approximately 33%. About 14% of an orally administered dose of Losartan is converted to the active metabolite, E-3174. Mean peak concentrations of Losartan and E-3174 are reached in 1 hour and in 3 to 4 hours, respectively. While maximum plasma concentrations of E-3174 is about 2 times higher than that for Losartan, the AUC of the metabolite is about 4 to 8 times as great as that of Losartan. Both Losartan and E-3174 are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. A plasma protein binding is constant over the concentration range achieved with recommended doses. When Losartan is 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 significantly to the elimination of Losartan and its metabolites.

Losartan is also found to have beneficial haemodynamic effects in heart failure. Pulmonary capillary wedge pressure and heart rate are found to be reduced and cardiac index is found to be increased with Losartan in patients with heart failure.

INDICATIONS

Tozaar is indicated in the treatment of mild to moderate hypertension alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Tozaar is contraindicated in patients who are hypersensitive to any component of this product. Losartan is also contraindicated in pregnancy and if pregnancy is detected, Tozaar should be discontinued immediately.

PRECAUTIONS

Intravascular volume depletion: In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. Such a condition should be corrected prior to administration of Tozaar, or a lower starting dose should be used.

Hepatic Impairment: Based on pharmacokinetic data, which demonstrate significantly increased plasma concentrations of Tozaar in cirrhotic patients; a lower dose should be considered for patients with a history of hepatic impairment.

Renal artery stenosis: Other drugs that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. While not confirmed, this potentially may occur with angiotensin-II receptor antagonists.

Use In Pregnancy, Nursing mothers and Children

Pregnancy

Although there is no experience with the use of Losartan in pregnant women, animal studies with Losartan have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be its effects on the renin-angiotensin-aldosterone system. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. Losartan is contraindicated in pregnancy, and if pregnancy is detected, Tozaar should be discontinued immediately.

Nursing Mothers

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

Children

Safety & efficacy in children have not been established.

ADVERSE REACTIONS

Side-effects with Losartan have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with Losartan was comparable to placebo.

In controlled clinical trials of essential hypertension, dizziness was the only drug related side effect that occurred with an incidence greater than placebo in 1% or more of patients treated with Losartan. In addition, dose-related orthostatic effects were seen in less than 1% of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo. In contrast to ACE inhibitors, Losartan is not found to cause accumulation of bradykinin and so incidence of cough observed with Losartan is significantly less as compared to ACE Inhibitors and is not more than that observed with placebo in several clinical trials.

DRUG INTERACTIONS

No drug interactions of clinical significance have been identified with Losartan. Compounds which have been studied in clinical pharmacokinetic trials include hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbitone.

DOSAGE & ADMINISTRATION

The starting and maintenance dose of Tozaar is 25 or 50mg once daily for most patients, with or without food. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose upto 100mg once daily.

Use in elderly: Patients up to 75 years: No initial dosage adjustment is necessary for this group of patients.

Patients over 75 years: At present there is limited clinical experience in this group; a lower starting dose of 25mg once daily is recommended.

Use in renal impairment: 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 25mg once daily is recommended.

Intravascular volume depletion: In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. Such a condition should be corrected prior to administration of Tozaar, or a lower starting dose should be used.

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 occurs, supportive treatment should be instituted. Neither Losartan nor the active metabolite E-3174 can be removed by haemodialysis.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

STORE BELOW 30^{o}C, PROTECTED FROM MOISTURE

PRESENTATION

Tozaar 25 : It is available as pink coloured, round, biconvex, film coated tablets, in strips of 7 tablets and also in strips of 10 tablets.
Tozaar 50 : It is available as pink coloured, round, biconvex, film coated tablets, in strips of 7 tablets and also in strips of 10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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