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

TOZAAR

(Losartan Potassium Tablets I.P.)

COMPOSITION

TOZAAR-25
Each film coated tablet contains:
Losartan Potassium I.P…….25mg
Colors: Red oxide of Iron and Titanium Dioxide I.P.

TOZAAR-50
Each film coated tablet contains:
Losartan Potassium I.P……50mg
Colors: Red oxide of Iron and Titanium Dioxide I.P.

WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue product as soon as possible.
Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

DOSAGE FORM

Film coated tablet

INDICATION

Tozaar is indicated in the treatment of mild to moderate hypertension.

DOSE AND METHOD OF ADMINISTRATION

Posology

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 thedose to 100 mg once daily (in the morning).

Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on bloodpressure response from one month onwards after initiation of therapy. Losartan may be administered with otherantihypertensive 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).

Special populations

Use in patients with intravascular volume depletion:

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.

Use in patients with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeuticexperience in patients with severe hepatic impairment. Therefore, losartan iscontraindicated in patients with severehepatic impairment.

Paediatric population
6 months – less than 6 years
The safety and efficacy of children aged 6 months to less than 6 years has not been established.

6 years to 18 years
For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. (Inexceptional cases the dose can be increased to a maximum of 50 mg once daily). Dosage should be adjustedaccording to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximumof 100 mg once daily. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in paediatricpatients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patientgroups.

It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2, as no data are available.

Losartan is also not recommended in children with hepatic impairment.

Use in Elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosageadjustment is not usually necessary for the elderly.

Method of administration
Losartan tablets should be swallowed with a glass of water.
Losartan tablets may be administered with or without food.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
The use of losartan is not recommended during the first trimester of pregnancy . The use of losartanis contraindicated during the 2nd and 3rd trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the firsttrimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there isno controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may existfor this class of medicinal products. Unless continued AIIRA therapy is considered essential, patients planningpregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile foruse in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, ifappropriate, alternative therapy should be started.
Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreasedrenal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension,hyperkalaemia).

Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renalfunction and skull is recommended.

Infants whose mothers have taken losartan should be closely observed for hypotension.

Lactation
Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommendedand alternative treatments with better established safety profiles during breastfeeding are preferable, especially whilenursing a newborn or preterm infant.

CONTRAINDICATIONS
• Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients
• Severe hepatic impairment
• 2^{nd} and 3^{rd} trimesters of pregnancy
• The concomitant use of losartanaliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

WARNINGS AND PRECAUTIONS
Hypersensitivity
*Angiooedema.*Patients with a history of angiooedema (swelling of the face, lips, throat, and/or tongue) should beclosely monitored.

Hypotension and Electrolyte/Fluid Imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients whoare volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Theseconditions should be corrected prior to administration of losartan, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should beaddressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemiawas higher in the group treated with losartan as

compared to the placebo group. Therefore, theplasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especiallypatients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing saltsubstitutes with losartan is not recommended.

Hepatic impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan incirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is notherapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not beadministered in patients with severe hepatic impairment.

Losartan is not recommended in children with hepatic impairment.

Renal impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure havebeen reported (in particular, in patients whose renal function is dependent on the renin- angiotensin-aldosteronesystem such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinalproducts that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine havealso been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; thesechanges in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution inpatients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in paediatric patients with renal impairment
Losartan is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2 as no data are available.

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This appliesparticularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renalfunction.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is notrecommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting throughinhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascularand cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other medicinal products acting on therenin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renalimpairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure andsymptomatic life-threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patientgroups. The combination of losartan with a beta-blocker should be used with caution.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, orobstructive hypertrophic cardiomyopathy.

Pregnancy
Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patientsplanning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safetyprofile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately,and, if appropriate, alternative therapy should be started.

Other warnings and precautions
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists areapparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higherprevalence of low-renin states in the black hypertensive population.

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 increasesthe risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade ofRAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore notrecommended

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, when drivingvehicles or operating machines it must be borne in mind that dizziness or drowsiness may occasionally occur whentaking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

DRUG INTERACTIONS

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with othersubstances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics,baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In aclinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite byapproximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolismenzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effectis unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor ofCYP2C9).

As with other medicinal products that block angiotensin II or its effects, concomitant use of othermedicinal productswhich retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increasepotassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead toincreases in serum potassium. Co-medication is not advisable.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitantadministration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptorantagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination provesessential, serum lithium level monitoring is recommended during concomitant use.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors,acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effectmay occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk ofworsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially inpatients with poor pre-existing renal function. The combination should be administered with caution, especially in theelderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function afterinitiation of concomitant therapy, and periodically thereafter.

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through thecombined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency ofadverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure)compared to the use of a single RAAS-acting agent.

UNDESIRABLE EFFECTS

Losartan has been evaluated in clinical studies as follows:

- In a controlled clinical trial in > 3,000 adult patients 18 years of age and older for essential hypertension
- In a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age

- In a controlled clinical trial in > 9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
- In controlled clinical trials in > 7,700 adult patients with chronic heart failure
- In a controlled clinical trial in > 1,500 type 2 diabetic patients 31 years of age and older with proteinuria

In these clinical trials, the most common adverse event was dizziness.

The frequency of adverse reactions listed below is defined using the following convention:very common (≥ 1/10); common (≥ 1/100, to < 1/10); uncommon (≥ 1/1,000, to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. The frequency of adverse reactions identified from placebo-controlled clinical studies and postmarketing experience

Adverse reaction	**Frequency of adverse reaction by indication**				**Other**
	Hypertension	**Hypertensive patients with left-ventricular hypertrophy**	**Chronic Heart Failure**	**Hypertension and type 2 diabetes with renal disease**	**Post-marketing experience**
Blood and lymphatic system disorders					
anaemia			common		frequency not known
thrombocytopenia					frequency not known
Immune system disorders					
hypersensitivity reactions, anaphylactic reactions, angiooedema*, and vasculitis**					rare
Psychiatric disorders					
depression					frequency not known
Nervous system disorders					
dizziness	common	common	common	common	
somnolence	uncommon				
headache	uncommon		uncommon		
sleep disorders	uncommon				
paraesthesia			rare		

migraine					frequency not known
dysgeusia					frequency not known
Ear and labyrinth disorders					
vertigo	common	common			
tinnitus					frequency not known
Cardiac disorders					
palpitations	uncommon				
angina pectoris	uncommon				
syncope			rare		
atrial fibrillation			rare		
cerebrovascular accident			rare		
Vascular disorders					
(orthostatic) hypotension (including dose-related orthostatic effects)‖	uncommon		common	common	
Respiratory, thoracic and mediastinal disorders					
dyspnoea			uncommon		
cough			uncommon		frequency not known
Gastrointestinal disorders					
abdominal pain	uncommon				
obstipation	uncommon				
diarrhoea			uncommon		frequency not known
nausea			uncommon		
vomiting			uncommon		
Hepatobiliary disorders					
pancreatitis					frequency not known
hepatitis					rare
liver function abnormalities					frequency not known
Skin and subcutaneous tissue disorders					

urticaria			uncommon		frequency not known
pruritus			uncommon		frequency not known
rash	uncommon		uncommon		frequency not known
photosensitivity					frequency not known
Musculoskeletal and connective tissue disorders					
myalgia					frequency not known
arthralgia					frequency not known
rhabdomyolysis					frequency not known
Renal and urinary disorders					
renal impairment			common		
renal failure			common		
Reproductive system and breast disorders					
erectile dysfunction / impotence					frequency not known
General disorders and administration site conditions					
asthenia	uncommon	common	uncommon	common	
fatigue	uncommon	common	uncommon	common	
oedema	uncommon				
malaise					frequency not known
Investigations					
hyperkalaemia	common		uncommon[†]	common[‡]	
increased alanine aminotransferase (ALT) [§]	rare				
increase in blood urea, serum creatinine, and serum potassium			common		
hyponatraemia					frequency not known

hypoglycaemia				common	

*Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some ofthese patientsangiooedema had been reported in the past in connection with the administration of other medicines,including ACE inhibitors

**Including Henoch-Schönleinpurpura

‖Especially in patients with intravascular depletion, e.g. patients with severe heart failure or under treatment with highdose diuretics

†Common in patients who received 150 mg losartan instead of 50 mg

‡In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartantablets developed hyperkalaemia>5.5 mmol/l and 3.4% of patients treated with placebo

§Usually resolved upon discontinuation

The following additional adverse reactions occurred more frequently in patients who received losartan than placebo(frequencies not known): back pain, urinary tract infection, and flu-like symptoms.

Renal and urinary disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renalfailure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuationof therapy.

Paediatric population
The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in thepaediatric population are limited.

OVERDOSE
Symptoms of intoxication
Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would behypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment of intoxication
If symptomatic hypotension should occur, supportive treatment should be instituted.

Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation ofthe cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activatedcharcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parametersshould be corrected if necessary.

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

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA01

Pharmacodynamic properties
Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, isthe primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology ofhypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenalgland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and therelease of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylicacid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route ofits synthesis.

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important incardiovascular regulation. Furthermore losartan does not inhibit ACE (kininase II), the enzyme that degradesbradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, removal of the angiotensin II negative feedback on renin secretion leads toincreased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despitethese increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained,indicating effective angiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin II valuesfell within three days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

Pharmacokinetic properties
Absorption
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an activecarboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets isapproximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4hours, respectively.

Distribution
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume ofdistribution of losartan is 34 litres.

Biotransformation
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Followingoral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily isattributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen inabout one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renalclearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan isadministered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted inthe urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartanpotassium 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, neitherlosartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites. Following an oraldose/intravenous administration of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in theurine and 58%/ 50% in the faeces.

Characteristics in patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differessentially from those found in young hypertensive patients.

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensivepatients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its activemetabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers.

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute.

Compared to patients with normal renal function, the AUC for losartan is about 2-times higher in haemodialysispatients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or inhaemodialysis patients.

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

Pharmacokinetics in paediatric patients

The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughlysimilar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschoolchildren, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to agreater extent between the age groups. When comparing preschool children with adolescents these differencesbecame statistically significant. Exposure in infants/ toddlers was comparatively high.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology,genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced adecrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum andoccasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinalchanges (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect therenin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development,resulting in foetal death and malformations.

EXPIRY DATE

Do not use later than the date of expiry.

PACKAGING INFORMATION

TOZAAR is available in blister of 10 Tablets.

STORAGE AND HANDLING INSTRUCTIONS

Store at a temperature not exceeding 30°c, protected from light and moisture. Keep all medicines out of reach of children.

MARKETED BY

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IN/TOZAAR/25,50/Apr-2015/04/PI