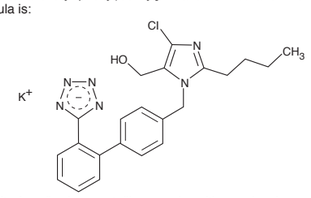
TOZAAR PLUS LS 50/12.5 MG TABLET

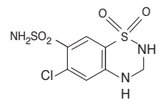
(Losartan Potassium and Hydrochlorothiazide Tablets)

COMPOSITION:
TOZAAR PLUS LS 50/12.5 MG TABLET
Each film coated tablet contains:
Losartan Potassium U.S.P. 50 mg
Hydrochlorothiazide Ph.Eur. 12.5 mg

DESCRIPTION:
Losartan potassium is an angiotensin II receptor (type AT1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl phenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.
Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

PHARMACOLOGICAL 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, noncompetitive 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. Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts.
Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics:
Losartan Potassium
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. 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 Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased). 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.
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 ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3 A4 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 volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. 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. 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 to the elimination of losartan and its metabolites.
Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.
Special Populations
Pediatric: Losartan pharmacokinetics have not been investigated in patients <18 years of age.
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.
Race: Pharmacokinetic differences due to race have not been studied.
Renal Insufficiency:
Losartan: 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.
Hydrochlorothiazide: Following oral administration, the AUC for hydrochlorothiazide is increased by 70 and 700% for patients with mild and moderate renal insufficiency, respectively.
In this study, renal clearance of hydrochlorothiazide decreased by 45 and 85% in patients with mild and moderate renal impairment, respectively.
The usual regimens of therapy with TOZAAR PLUS may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so TOZAAR PLUS is not recommended.
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. The lower starting dose of losartan recommended for use in patients with hepatic therefore, not recommended.

DRUG INTERACTIONS:
Losartan Potassium
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.
Hydrochlorothiazide
When administered concurrently, the following drugs may interact with thiazide diuretics: Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.
Antidiabetic drugs (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.
Other antihypertensive drugs - additive effect or potentiation.
Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g., norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - possible increased responsiveness to the muscle relaxant.
Lithium — should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Non-steroidal Anti-inflammatory Drugs including Selective Cyclooxygenase-2 Inhibitors - In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when FDC of Losartan Potassium and Hydrochlorothiazide and non-steroidal anti-inflammatory agents including selective cyclooxygenase-2 inhibitors are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

SIDE EFFECTS:
Treatment with losartan potassium-hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. The following adverse experiences reported with Losartan potassium hydrochlorothiazide occurred in ≥1 percent of patients, and more often on drug than placebo, regardless of drug relationship:

	Losartan Potassium Hydrochlorothiazide (n=858)	Placebo (n= 173)
Body as a Whole		
Abdominal Pain	1.2	0.6
Edema/Swelling	1.3	1.2
Cardiovascular Disorders		
Palpitation	1.4	0.0
Musculoskeletal		
Back Pain	2.1	0.6
Nervous / Psychiatric disorders		
Dizziness	5.7	2.9
Respiratory		
Cough	2.6	2.3
Sinusitis	1.2	0.6
Upper Respiratory infection	6.1	4.6
Skin		
Rash	1.4	0.0

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group in studies of essential hypertension: asthenia/fatigue, diarrhea, nausea, headache, bronchitis, pharyngitis.
Losartan Potassium
Other adverse experiences that have been reported with losartan, without regard to causality, are listed below:
Body as a Whole: chest pain, facial edema, fever, orthostatic effects, syncope;
Cardiovascular: angina pectoris, arrhythmias including atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia and ventricular fibrillation, CVA, hypotension, myocardial infarction, second degree AV block;
Digestive:anorexia, constipation, dental pain, dry mouth, dyspepsia, flatulence, gastritis, vomiting;
Hematologic: anemia;
Metabolic: gout;
Musculoskeletal: arm pain, arthralgia, arthritis, fibromyalgia, hip pain, joint swelling, knee pain, leg pain, muscle cramps, muscle weakness, musculoskeletal pain, myalgia, shoulder pain, stiffness;
Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, insomnia, libido decreased, memory impairment, migraine, nervousness, panic disorder, paresthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo;
Respiratory: dyspnea, epistaxis, nasal congestion, pharyngeal discomfort, respiratory congestion, rhinitis, sinus disorder;
Skin: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, sweating, urticaria;
Special Senses: blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity, taste perversion, tinnitus;
Urogenital: impotence, nocturia, urinary frequency, urinary tract infection.
Hydrochlorothiazide
Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body as a Whole: weakness;
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation;
Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia;
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema;
Metabolic: hyperglycemia, glycosuria, hyperuricemia;
Musculoskeletal: muscle spasm;
Nervous System/Psychiatric: restlessness;
Renal: renal failure, renal dysfunction, interstitial nephritis;
Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;
Special Senses: transient blurred vision, xanthopsia.
Persistent dry cough (with an incidence of a few percent) has been associated with ACE-inhibitor use and in practice can be a cause of discontinuation of ACE-inhibitor therapy.

INDICATIONS:
TOZAAR PLUS LS is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.
Hypertensive patients with left Ventricular Hypertrophy-TOZAAR PLUS LS is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

CONTRA-INDICATIONS:
TOZAAR PLUS is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

DOSAGE AND DIRECTIONS FOR USE:
Fixed dose combination is not indicated for initial therapy.
i. Tozaar Plus should not be initiated in patients who are intravascularly volume-depleted (eg: those treated with high-dose diuretics)
ii. Tozaar Plus should not be used as initial therapy in elderly patients
Hypertension
Usual starting & maintenance dose: 1 tab of TOZAAR PLUS 50/12.5 mg once daily. May be increased to 2 tab of TOZAAR PLUS 50/12.5 mg once daily. Maximum: 2 tab of TOZAAR PLUS 50/12.5 mg once daily.
Hypertensive patients with left ventricular hypertrophy
Usual starting dose: 50 mg losartan once daily may be titrated with a combination of losartan and hydrochlorothiazide 12.5mg, increased if necessary to losartan 100mg and hydrochlorothiazide 25mg once daily.
Use in Patients with Renal Impairment: The usual regimens of therapy with TOZAAR PLUS Maybe followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so TOZAAR PLUS is not recommended.
Patients with Hepatic Impairment: TOZAAR PLUS is not recommended for titration in patients with hepatic impairment (see WARNINGS, *Impaired Hepatic Function*) because the appropriate 25 mg starting dose of losartan cannot be given.

PREGNANCY AND LACTATION:

Warning:
ACE inhibitors have been shown to be strongly fetotoxic in animal studies. Recently available data indicate that ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant woman. The use of these agents during pregnancy is not recommended.

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.

SPECIAL WARNINGS AND PRECAUTIONS
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, TOZAAR PLUS 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 TOZAAR PLUS 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, TOZAAR PLUS 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.
There was no evidence of teratogenicity in rats or rabbits treated with a maximum losartan potassium dose of 10 mg/kg/day in combination with 2.5 mg/kg/day of hydrochlorothiazide. At these dosages, respective exposures (AUCs) of losartan, its active metabolite, and hydrochlorothiazide in rabbits were approximately 5, 1.5, and 1.0 times those achieved in humans with 100 mg losartan in combination with 25 mg hydrochlorothiazide. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs, was observed when females were treated prior to and throughout gestation with 10 mg/kg/day losartan in combination with 2.5 mg/kg/day hydrochlorothiazide. As also observed in studies with losartan alone, adverse fetal and neonatal effects, including decreased body weight, renal toxicity, and mortality, occurred when pregnant rats were treated during late gestation and/or lactation with 50 mg/kg/day losartan in combination with 12.5 mg/kg/day hydrochlorothiazide. Respective AUCs for losartan, its active metabolite and hydrochlorothiazide at these dosages in rats were approximately 35, 10 and 10 times greater than those achieved in humans with the administration of 100 mg of losartan in combination with 25 mg hydrochlorothiazide. When hydrochlorothiazide was administered without losartan to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day, respectively, there was no evidence of harm to the fetus. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
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 TOZAAR PLUS. This condition should be corrected prior to administration of TOZAAR PLUS (see DOSAGE AND ADMINISTRATION).
Impaired Hepatic Function
Losartan Potassium-Hydrochlorothiazide
TOZAAR PLUS is not recommended for patients with hepatic impairment who require titration with losartan. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using TOZAAR PLUS.
Hydrochlorothiazide
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Hypersensitivity Reaction
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
Lithium Interaction
Lithium generally should not be given with thiazides (see *Drug Interactions, Hydrochlorothiazide, Lithium*).

PRECAUTIONS
General
Hypersensitivity: Angioedema. See ADVERSE REACTIONS, *Post-Marketing Experience.*
Losartan Potassium-Hydrochlorothiazide
In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 6.7% versus 3.5% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. No patient discontinued due to increases or decreases in serum potassium. The mean decrease in serum potassium in patients treated with various doses of losartan and hydrochlorothiazide was 0.123 mEq/L.
In patients treated with various doses of losartan and hydrochlorothiazide, there was also a dose-related decrease in the hypokalemic response to hydrochlorothiazide as the dose of losartan was increased, as well as a dose-related decrease in serum uric acid with increasing doses of losartan.
Hydrochlorothiazide
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.
All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.
Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).
Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.
Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening.
In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.
In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required.
Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.
The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.
Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.
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 losartan; 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 losartan.
In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with losartan; in some patients, these effects were reversible upon discontinuation of therapy.
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

OVERDOSAGE AND THEIR MANAGEMENT:
Losartan Potassium
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 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 its active metabolite can be removed by hemodialysis.
Hydrochlorothiazide
The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

IDENTIFICATION:
TOZAAR PLUS LS 50/12.5 MG TABLET : Light Yellow colored, oval shaped, biconvex film coated tablets with break line on both the sides.

STORAGE INSTRUCTIONS:
Store below 25°C, protect from light.

PRESENTATION:
TOZAAR PLUS LS 50/12.5 MG TABLET are packed in blister pack using white opaque triplex film PVC/LDPE/PVdC film of 10 tablets.Such blisters containing 10 tablets are packed in to a carton of 10s, 30s and 100s.
Not all presentations may be available locally.

DATE OF REVISION
12 December, 2012

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.