Hepatic insufficiency: Initial dose for Losartan should be reduced by half in patients with history of hepatic disease.

Hydrochlorothiazide
Diuretic effect of Hydrochlorothiazide starts after 2 hours following oral intake, reaches to maximum levels in 4 hours and lasts for 6-12 hours. Hydrochlorothiazide does not metabolize, it is excreted through kidneys in a short time. Plasma half life varies between 5.6 – 14.8 hours. At least 61% of a single oral dose is excreted in urine unchanged in 24 hours.

INDICATIONS:
LOSARTES PLUS is indicated for the treatment of hypertension in patients when combination therapy is needed.

CONTRAINDICATIONS:
LOSARTES PLUS Film Tablet is contraindicated in patients who are hypersensitive to any component of this drug product. Additionally, it should not be used in patients with anuria and hypersensitivity to other sulfonamide-derived drugs.

WARNINGS / PRECAUTIONS:
Since renal perfusion of fetus starts in the second trimester of pregnancy due to maternal renin-angiotensin system, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus when used during the second and third trimester.

Hypovolemia - Hypotension
LOSARTES PLUS treatment should not be initiated in patients with intravascular volume reduction and electrolyte balance disorder prior to correction of fluid and electrolyte balance.

Losartan Potassium
Hepatic impairment:
LOSARTES PLUS should not be initiated in patients with hepatic impairment necessitating Losartan dose adjustment.

Renal impairment:
As Losartan inhibits the renin-angiotensin system, changes in renal function may appear in hypersensitive patients. These changes are reversible and return to normal upon discontinuation of therapy.

In patients of whom kidney functions are maintained with renin-angiotensin-aldosterone system support (i.e. advanced heart failure) Losartan treatment can cause progressive azothemia, oliguria, renal impairment and death.

In patients with unilateral or bilateral renal artery stenosis, Losartan can cause elevated creatinine and blood urea nitrogen (BUN). This elevation may be reversible in some patients.

Hydrochlorothiazide
There can be disorders in fluid and electrolyte balances in patients receiving thiazide compounds. The main disorders can be listed as follows: hyponatremia, hypochloremic alkalosis and hypokalemia. Especially in patients with vomiting and diarrhea or receiving parenteral fluids, serum electrolyte levels must be tested.

In long term treatments, especially if diuresis is strong or there is advanced sirosis, hypokalemia may develop.

Dilusional hyponatremia can be seen in patients with edema as a result of salt loss and extensive water intake due to extreme hot weathers. As for treatment water intake should be limited. In case of severe salt loss, additional salt must be administered.

Hypochloremic alkalosis is rare. It appears only if other metabolic and renal diseases develop. Chloride compounds are given as treatment. Even though thiazides cause hyperurisemia, Losartan's uricosuric effect will moderate this.

Thiazide treatment can deteriorate glucose tolerance. There may be a need to adjust doses for insulin or oral hypoglycemic agents in diabetic patients. Thiazides can convert latent diabetes to manifested diabetes.

Thiazides decrease calcium excretion with urine and consequently cause slight increase in serum calcium levels. If hypercalcemia is severe, parathyroid function must be assessed.

Thiazides increase magnesium excretion with resultant hypomagnesemia.

Use in Pregnancy and Lactation:

Use in pregnancy:
Pregnancy category C: First trimester
Pregnancy category D: Second and third trimester

Since renal perfusion of fetus starts in the second trimester of pregnancy due to maternal renin-angiotensin system, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus when used during the second and third trimester.

When the fetus is exposed to the drug in the first trimester, no adverse effect of Losartan is observed on the fetus. This should be explained to mothers exposed to the drug in the first trimester. However in patients who become pregnant when using the drug, drug administration should be terminated immediately. Losartan can only be used during the second and third trimester if no alternative treatment is available and only if the mother's life is in danger.

Thiazides can pass through placenta barrier to umbilical cord blood stream.

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Use in lactation:
No information is available regarding the excretion of Losartan in human milk. Thiazides are excreted in human milk. A decision should be made whether to discontinue nursing or administration of the drug, taking into account the importance of the drug to the mother.

Pediatric patients:
Safety and efficacy of Losartan have not been demonstrated in pediatric patients.

Geriatric patients:
In controlled studies safety and efficacy of Losartan did not show any difference between pediatric and geriatric patients.

SIDE EFFECTS / ADVERSE EFFECTS:
During treatments with LOSARTES PLUS, no additional side effects other than the effects seen with Losartan and Hydrochlorothiazide were observed. Generally, Losartan Potassium – Hydrochlorothiazide combination is well tolerated.

Most of the adverse reactions are mild and transient, so they do not necessitate termination of the treatment.

Following are the adverse reactions seen over 1% in clinical studies and more often than placebo groups: Abdominal pain, edema, palpitation, back pain, dizziness, cough, sinusitis, upper respiratory infection and rash.

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Angioedema, Henoch-Schönlein purpura and anaphylactic reactions have been reported rarely.

Hematological effects: Anemia.

Digestive system: Anorexia, dry mouth, diarrhea, constipation and rarely hepatitis have been reported.

Skin: Urticaria, alopecia, dermatitis, dry skin, ecchymosis, erythema, photosensitivity, pruritus, rash, sweating.

Respiratory system: Dyspnea, dry cough, bronchitis, epistaxis, rhinitis, respiratory congestion.

Hyponatremia and hyperkalemia have been reported with Losartan.

Other adverse reactions seen with any compound of LOSARTES PLUS and have the potential to be seen with LOSARTES PLUS tablets are as follows:

Losartan Potassium
Orthostatic effects, asthenia, fatigue, tachycardia, muscle cramp, cough, anemia, myalgia.

Hydrochlorothiazide
Anorexia, nausea, vomiting, diarrhea, constipation, cholestatic hepatitis, vertigo, paresthesia, hyponatremia, renal insufficiency, muscle spasm, blurred vision, hyperglycemia.

IN THE EVENT OF AN UNEXPECTED REACTION CONSULT YOUR PHYSICIAN

DRUG INTERACTIONS:

Losartan Potassium
No drug-drug interactions have been found in clinical pharmacokinetic studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital.

Although potent inhibitors of Cytochrome P450 2C9 3A4 systems (ketoconazole, troleandomicine, gestoden, sulphaphenazol) have not been clinically investigated, they have inhibited in vitro conversion of Losartan to its active metabolite to a large extent. As with other drugs that block angiotensin II effects, concomitant use of Losartan with potassium-sparing diuretics (spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium levels.

As seen with other antihypertensive drugs, antihypertensive effect of Losartan can be reduced with indomethasine, a nonsteroidal anti-inflammatory drug.

Hydrochlorothiazide
The following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Orthostatic hypotension may develop.

Antidiabetic drugs (oral, insulin): Dosage adjustment of the antidiabetic drug may be required.
Other antihypertensive drugs: Additive effect is expected.
Cholestyramine and colestipol: Cholestyramine or colestipol bind the hydrochlorothiazide and reduce its absorption up to 85 and 43 percent, respectively.
Corticosteroids, ACTH: May lead to electrolyte loss and particularly hypokalemia.
Pressor amines (e.g., norepinephrine): Hypertensive effects may decay but this decay do not avert their use.
Nondepolarizing myorelaxants (e.g., tubocurarine): Response to these relaxants may increase.