Lithium: In general, concomitant use with diuretics is not recommended. Diuretics reduce the renal clearance of lithium and increase the risk of toxicity by increasing blood levels.

Non-steroidal Anti-inflammatory drugs: May reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. When used concomitantly, the patient should be observed closely.

METHOD OF ADMINISTRATION AND DOSAGE:
Routine initial and maintenance dose for LOSARTES PLUS unless directed otherwise by a physician is 1 tablet daily (Losartan Potassium 50 mg / Hydrochlorothiazide 12.5 mg). In case of inadequate response, the dose can be elevated to 2 tablets once daily (Losartan Potassium 100 mg / Hydrochlorothiazide 25 mg). This is also the daily maximum dose. Antihypertensive effect is usually seen within 3 weeks of treatment initiation.

LOSARTES PLUS should not be initiated in patients with intravascular volume loss (i.e. patients using high dose diuretics).

LOSARTES PLUS should not be administered to patients with renal impairment whose creatinine clearance is below 30 mL/min.

LOSARTES PLUS should not be used in patients with hepatic impairment.

LOSARTES PLUS may be used in elderly patients without any dosage adjustment.

LOSARTES PLUS may be administered with other antihypertensive agents.

LOSARTES PLUS may be administered with or without food.

OVERDOSE AND PRECAUTIONS:
No specific information is available on the treatment of overdosage with Losartan Potassium – Hydrochlorothiazide combination. In that case, symptomatic and supportive treatment is applied.

Drug is removed from the stomach by emesis or gastric lavage. Possible dehydration, electrolyte imbalance, hepatic coma and hypotension should be treated with appropriate methods.

Losartan Potassium
Limited data are available in regard to overdosage in humans. Hypotension and tachycardia are the most likely manifestation of overdosage. Bradycardia could occur from vagal stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The most common symptoms observed are hypokalemia, hypochloremia, hyponatremia and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may augment the arrhythmias caused by digitalis. The degree of hydrochlorothiazide which can be removed by hemodialysis has not been established.

STORAGE CONDITIONS:
Keep out of the reach of children.
Store in its original package at room temperature below 25°C in a dry place.
Protect from light.

HOW SUPPLIED:
LOSARTES PLUS 100 mg / 25 mg Film Coated Tablet, in blister packs of 28 film coated tablets

OTHER AVAILABLE PHARMACEUTICAL DOSAGE FORMS:
LOSARTES PLUS 50 mg / 12.5 mg Film Coated Tablet, in blister packs of 28 film coated tablets

PRODUCT LICENCE HOLDER:
The holder of trade mark and marketing authorization holder
BioActiveT United Kingdom

For prescription only.

BioActiveT United Kingdom

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LOSARTES PLUS 100 mg/25 mg FILM COATED TABLET

FORMULA: Each film coated tablet contains:
100 mg Losartan Potassium and 25 mg Hydrochlorothiazide.
Titanium dioxide, Quinoline yellow Al. lacquer, Yellow iron oxide and FD&C Yellow #6 / Sunset yellow FCF Al. lacquer were used as coloring agents.

PHARMACOLOGICAL PROPERTIES:
LOSARTES PLUS is the combination of an angiotensin II receptor (AT_1) antagonist, Losartan Potassium and a thiazide diuretic, Hydrochlorothiazide.

Pharmacodynamic Properties:
Losartan Potassium
Losartan is a non-peptid angiotensin-II receptor (type AT_1) antagonist. Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin-II and acts as a antihypertensive agent by binding selectively to the AT_1 receptors together with its active metabolite transformed in the body. In vitro studies indicate that Losartan is a reversible and competitive inhibitor of the AT_1 receptor; the active metabolite is 10 to 40 times more potent than Losartan and appears to be a reversible non-competitive inhibitor of the AT_1 receptor.

Angiotensin II causes vasoconstriction in smooth vasculature, elevates blood pressure, stimulates aldosterone and vasopressin excretions, stimulates sympathetic system and increases thirst. All of these physiological effects of Angiotensin II are inhibited by Losartan and its active metabolite.

Losartan and its active metabolite bind to the AT_1 receptors with high selectivity (1000 fold higher than AT_2) and do not bind to other hormone receptors or ion channels significant for cardiovascular regulation.

Following Losartan administration in therapeutic doses, blood pressure decreases, renin and angiotensin II levels increase, aldosterone decreases and potassium level remains unchanged.

Renal glomerular filtration speed and filtration fraction remain constant, renal plasma flow increases and plasma lipid profile doesn't change.

Glucose consumption index and insulin sensitivity increase, uricosuric effect is observed.

Hydrochlorothiazide
Is a diuretic from Thiazide class. Acts as a antihypertensive by itself. If administered with Losartan, this effect strengthens. Hydrochlorothiazide effects electrolyte metabolism and provides excretion of equal amounts of sodium and chloride in distal renal tubular. As the result of diuretic effect of Hydrochlorothiazide, plasma volume and serum potassium levels decrease; renin-angiotensin-aldosterone system activates; plasma renin activity, aldosterone secretion and potassium excretion with urine increase.

Since Losartan blocks renin-angiotensin-aldosterone system on angiotensin II (AT_1) receptors, potassium losses caused by aldosterone are avoided.

In addition, Losartan antagonizes hyperurisemic effect of Hydrochlorothiazide via its uricozuric effect.

Antihypertensive effect of LOSARTES PLUS lasts for 24 hours and antihypertensive efficacy is maintained with long term use. Losartan - Hydrochlorothiazide combination (50 mg / 12.5 mg), has been provided a mean 13.2 mm Hg decrease in diastolic blood pressure in sitting position in a 12 week single dose daily clinical study.

Pharmacokinetic Properties:
Losartan Potassium
Absorption: Following oral administration, losartan is well absorbed and undergoes first-pass metabolism in the liver. The systemic bioavailability of is approximately 33%. Losartan and its active metabolite reach to mean peak concentrations 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution: Both losartan and its metabolite are highly (≥ 99%) bound to plasma proteins (primarily albumin). The volume of distribution of losartan is 34 liters.

Metabolism: Losartan converts to several inactive metabolites besides active carboxylic acid metabolite. Cytochrome P450 2C9 and 3A4 enzymes make this possible.

Excretion: Total plasma clearance of losartan and its active metabolite is 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is 70 mL/min and 25 mL/min, respectively. When losartan is administered orally, 4% of the dose is excreted unchanged in the urine, and 6% of the dose is excreted in the urine as active metabolite. Both biliary and urinary excretion contributes to the elimination of losartan and its metabolites. Following an oral dose of 14C-labelled losartan, 35% of radioactivity is recovered in the urine and 60% in the faeces.

Special patient populations:
Pediatric patients: Losartan pharmacokinetics has not been investigated in patients under 18 years old.

Geriatric patients: Blood levels of elderly (≥ 65-75 years) patients are the same as those in young patients, thus no dose adjustment is required.

Renal insufficiency: If the creatinine clearance is above 30 mL/min in renal patients blood levels remain unchanged. If the creatinine clearance is lower, EAA is increased by 50%, in hemodialysis patients it doubles. Neither Losartan nor the active metabolite can be removed from blood with hemodialysis. Dose adjustment is not necessary except hypovolemia.

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.