LOSARTAN potassium + HYDROCHLOROTHIAZIDE

NEOSARTAN® *plus*

50mg / 12.50mg Film-coated Tablet

ANGIOTENSIN II RECEPTOR BLOCKER / DIURETIC

FORMULATION:

Each Film-coated tablet contains:

Losartan potassium..... 50 mg

Hydrochlorothiazide..... 12.50 mg

PRODUCT DESCRIPTION:

-Physical Properties: White to off-white, round, biconvex, film-coated tablet, plain on both sides.

-Chemical Name:

Losartan potassium: 2-Butyl-4-chloro-1-[*p*-o-1*H*-tetrazol-5-ylphenyl)benzyl] imidazole-5-methanol, potassium

Hydrochlorothiazide: 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

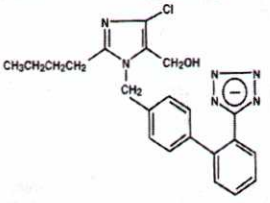
- Molecular Weight:

Losartan potassium: 461.0

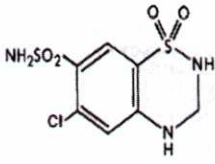
Hydrochlorothiazide: 297.7

-Empirical Formula / Structural Formula:

Losartan potassium: $C_{22}H_{22}ClKN_6O$



Hydrochlorothiazide: $C_7H_8ClN_3O_4S_2$



PHARMACODYNAMICS / PHARMACOKINETICS:

Losartan potassium: It is an angiotensin II receptor blocker with antihypertensive activity due mainly to selective blockage of AT_1 receptors and the consequent reduced pressure effect of angiotensin II.

Losartan potassium is readily absorbed from the gastrointestinal tract following oral administration, with an oral bioavailability of about 33%. It undergoes first-pass metabolism to form an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan, and some inactive metabolites. Metabolism is primarily by cytochrome P450 isoenzyme CYP2C9 and CYP3A4. Peak plasma concentrations of losartan, and E-3174 occur about 1 hour and 3 to 4 hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the feces via bile, as unchanged drug and metabolites. Following oral dosing about 35% of the dose is excreted in the urine and about 60% in the feces. The terminal elimination half-lives of Losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours respectively.

Hydrochlorothiazide: It is a diuretic antihypertensive. It is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65% to 70%. It has been estimated to have a plasma half-life of between about 5 to 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placenta barrier and is distributed into breast milk.

INDICATIONS:

Losartan potassium is used in the management of hypertension and may have a role in patients who develop cough with ACE (Angiotensin Converting Enzyme) inhibitors.

Hydrochlorothiazide is used in the treatment of edema associated with heart failure and with renal hepatic disorders. It is also used in hypertension, either alone or together with other antihypertensives such as ACE inhibitors and beta blockers.

Hydrochlorothiazide is also indicated in the treatment of edema accompanying premenstrual syndrome, prevention of water retention associated with corticosteroid and estrogens, treatment of diabetes insipidus, and prevention of renal calculus formation in patients with hypercalciuria.

DOSAGE AND ADMINISTRATION:

An initial dose of 25mg once daily may be used in the elderly over 75 years old and for patients with moderate to severe renal impairment (creatinine clearance less than 20 mL per minute), or intravascular fluid depletion.

Usual dose: Losartan potassium 50 mg / hydrochlorothiazide 12.50 mg once daily. The dose may be increased, if necessary, to 100 mg / 25 mg daily as single dose or in two divided doses. Or, as prescribed by a physician.

CONTRAINDICATIONS:

It must not be given to pregnant women because it crosses the placenta and is distributed in breast milk.

Hydrochlorothiazide is not effective in patients with creatinine clearance of less than 30 mL per minute and thus should not be given to patients with severe renal impairment or anuria. It is also contraindicated with Addison's disease. Thiazide can reduce urinary excretion of calcium, sometimes resulting in mild hypercalcemia and is therefore contraindicated to patients with pre-existing hypercalcemia.

WARNINGS AND PRECAUTIONS:

It should be used with caution in patients with renal artery stenosis / renal impairment since it can further reduce renal function. Patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.

An increased risk of non-melanoma skin cancer (NMSC), basal cell carcinoma and squamous cell carcinoma, with increasing cumulative dose of hydrochlorothiazide exposure has been observed in 2 epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism of NMSC.
Patients taking Hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

DRUG INTERACTIONS:
Losartan potassium: In clinical trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (phenobarbitone), (see Hydrochlorothiazide; Alcohol, barbiturates, or narcotics below) ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences have not been evaluated.
As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. Potassium sparing diuretics, potassium supplements, or salt substitutes containing potassium) may lead to increase in serum potassium.
Hydrochlorothiazide: When given 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 – there may be an additive effect
Cholestyramine and colestipol resins – absorption of hydrochlorothiazide is impaired in the presence of anionic exchanged resins.
Corticosteroids, ACTH (Adrenocorticotropic Hormone) – there may be intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g. adrenaline) – possible decreased response to pressor amines, but not sufficient to preclude their use.

PREGNANCY AND LACTATION:
It is contraindicated in pregnancy since it has been associated with fetal toxicity in animal studies. Other drugs such as ACE (Angiotensin Converting Enzyme) inhibitors that act on the renin-angiotensin system have been associated with fetal toxicity in humans.

ADVERSE EFFECTS:
Losartan potassium: Adverse effects include dizziness and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received high-dose diuretics). Losartan potassium may cause hyperkalemia in patients with renal disease. Other adverse effects that have been reported with angiotensin II receptor antagonist include respiratory tract disorder, back pain, gastrointestinal disturbances, fatigue, and neutropenia.
Hydrochlorothiazide: Thiazide diuretics may cause a number of metabolic disturbances especially at high doses. They may provoke hyperglycemia and glycosuria in diabetic and other susceptible patients. They may cause hyperuricemia and precipitate attacks of gout in some patients. Administration of hydrochlorothiazide may be associated with electrolyte imbalances including hypochloremic alkalosis, hyponatremia, hypokalemia. Hypokalemia intensifies the effect of digitalis on cardiac muscle and administration of digitalis or its glycoside may be temporarily suspended. Patients with cirrhosis of the liver are particularly at risk from hypokalemia.

OVERDOSE AND TREATMENT:
Losartan potassium: Significantly, lethality was observed in mice & 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/m^2 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 potassium nor its active metabolites can be removed by hemodialysis.
Hydrochlorothiazide: The oral LD_{50} (Lethal $Dose_{50}$) of hydrochlorothiazide is greater than 10g/kg in both mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) 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.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C. Protect from light.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Patient should seek medical attention immediately at the first sign of any adverse drug reaction.

AVAILABILITY:
50 mg /12.50 mg Film-coated Tablet Foil Strip x 10's (Box of 30's) – DR-XY35708

DATE OF FIRST AUTHORIZATION:
June 04, 2010

DATE OF REVISION OF PACKAGE INSERT:
October 2021

NEOSARTAN® is a registered mark of GX INTERNATIONAL, INC.

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