Hydrochlorothiazide

Hytaz®

12.5 mg & 25 mg Film Coated Tablet

Diuretic / Antihypertensive

℞

FORMULATIONS
Each film-coated tablet contains:
Hydrochlorothiazide ..... 12.5 mg or 25 mg

PRODUCT DESCRIPTIONS
Hytaz® 12.5 mg Tablet: Yellow, biconvex and film-coated tablet
Hytaz® 25 mg Tablet: Yellow, biconvex, film-coated tablet, bisected on one side and plain on the other side

CLINICAL PHARMACOLOGY
• PHARMACODYNAMICS
Hydrochlorothiazide (HCTZ), a thiazide diuretic, increases the excretion of water by inhibiting the reabsorption of sodium and chloride ions at the distal renal tubule. The excretion of potassium and magnesium is also increased while the elimination of calcium and uric acid is decreased. Thiazide diuretics usually do not affect normal blood pressure. When chronically administered, thiazide diuretics decrease peripheral vascular resistance. The exact mechanism responsible for lowered peripheral resistance is not known, however, excretion of urinary sodium by the kidneys is required to achieve blood pressure reduction.
Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion, urinary potassium loss, and decrease 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 HCTZ.
Diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours after oral administration of HCTZ.

• PHARMACOKINETICS
HCTZ is well absorbed from the gastrointestinal tract. Oral bioavailability is approximately 65 to 75%. The drug crosses the placenta, but not the blood-brain barrier and is distributed in breast milk. It appears to be preferentially bound to red blood cells. HCTZ is not metabolized but is eliminated rapidly as unchanged drug in the urine. HCTZ's elimination half-life ranged from 5.6 to 15 hours when plasma levels were followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

INDICATIONS
• Edema associated with congestive heart failure, hepatic cirrhosis, corticosteroid and estrogen therapy
• Edema due to various forms of renal dysfunction (e.g., nephritic syndrome, acute glomerulonephritis, and chronic renal failure)
• Control of essential hypertension

DOSAGE AND ADMINISTRATION
Hydrochlorothiazide is administered orally.

Individualize therapy according to patient response. Use the smallest dosage necessary to achieve the required response.

Edema:
Usual Initial Dose: 25 – 200 mg daily in 1 – 3 divided doses
Maintenance Dose: 25 – 100 mg daily as single or divided doses

Hypertension:
Usual Initial Adult Dose: 12.5 – 50 mg once daily
Maintenance Dose: 25 – 100 mg once daily
or, as prescribed by the physician.

CONTRAINDICATIONS
• Hypersensitivity to any component of the product or to other sulfonamide-derivatives
• Anuria

WARNINGS AND PRECAUTIONS
Hypotension and Fluid/Electrolyte Imbalance: As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance (e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia, or hypokalemia) which may occur particularly during intercurrent diarrhea or vomiting. Serum electrolytes should be monitored regularly.
Signs and symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances including nausea and vomiting.
Hypokalemia may develop, particularly with brisk diuresis, when liver 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 situations (e.g., liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.
Dilutional hyponatremia may be seen in edematous patients in hot weather. Appropriate treatment is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. Appropriate replacement therapy is the treatment of choice in actual salt depletion.
Renal Disease: Use with caution in patients with severe renal disease because thiazides may precipitate azotemia.
Hepatic Disease: Use with caution in patients with hepatic disease or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic encephalopathy.
Hypersensitivity Reaction: Hypersensitivity reactions to HCTZ may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. As a sulfonamide derivative, HCTZ can cause skin rashes and blood dyscrasias.
Systemic Lupus Erythematosus: Exacerbation or activation of systemic lupus erythematosus has been associated with the use of thiazide diuretics.
Metabolic and Endocrine Effects:
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.
Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Discontinue thiazides before taking parathyroid function test.
Thiazide diuretic therapy may increase cholesterol and triglyceride levels.
Hyperuricemia may occur or acute gout may be precipitated in certain patients taking thiazide therapy.
Thiazides have been reported to increase the urinary excretion of magnesium. This may result in hypomagnesemia.

INTERACTIONS WITH OTHER MEDICAMENTS
Administration of the following drugs may interact with thiazide diuretics:
Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may be observed
Amantadine: Increased risk of adverse effects
Anticholinergic agents (e.g., atropine, biperidine): May increase availability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate
Antidiabetic medicines (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be necessary
Other antihypertensive drugs: Additive effect or potentiation
Cholestyramine and colestipol resins: HCTZ absorption is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind HCTZ and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.
Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia
Cytotoxic agents: Decreased renal excretion; increased myelosuppresive effects
Pressor amines (e.g., adrenaline): Possible decreased response to pressor amines but not sufficient to prevent their use
Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant
Lithium: Volume depletion increases lithium absorption and may cause lithium toxicity, unless levels are closely monitored and dosage reduced accordingly. Conversely, sudden stopping of diuretic treatment may result in a sub-therapeutic level of circulating lithium.
Non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 Inhibitors: The administration of NSAIDs including selective COX-2 inhibitors can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Thiazides must be avoided during the first trimester of pregnancy
Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.
Lactation: Thiazides appear in human breast milk. A decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

UNDESIRABLE EFFECTS
Body as a Whole: Weakness, fatigue
Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics, antihypertensive drugs), transient cerebral ischemic attacks
Gastrointestinal: Anorexia, gastric irritation, nausea, vomiting, sialadenitis, cramping, diarrhea, constipation, intrahepatic cholestatic jaundice, pancreatitis
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
Hypersensitivity reactions: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, purpura, urticaria
Metabolic and Nutritional: Hypokalemia, hyponatremia, hypochloremic alkalosis, hypophosphatemia, hypomagnesemia, hypercalcemia, hyperglycemia, impairment of glucose tolerance, glycosuria, increases in total cholesterol, low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c) and triglycerides
Musculoskeletal: Muscle spasm
Nervous System: Restlessness,dizziness, vertigo, paresthesia, headache
Urinary: Renal impairment, renal failure, interstitial nephritis
Skin: Rash, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, polyarteritis nodosa, alopecia
Urogenital: Impotence
Others: Fever, transient blurred vision, xanthopsia

OVERDOSE AND TREATMENT
The most common signs and symptoms of HCTZ overdose include electrolyte imbalance (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. Other features of overdose are lethargy, nausea and weakness. Lethargy may progress to coma within a few hours with minimal depression of respiratory and cardiovascular function without evidence of dehydration or serum electrolyte changes. Gastrointestinal irritation and hypermotility may occur, and temporary elevation of blood urea nitrogen has been reported.
In the treatment of thiazide overdosage, gastric contents may be evacuated taking caution to avoid aspiration, particularly in unconscious patients. If the patient is conscious, induction of vomiting with ipecac syrup is effective in removing the drug from the stomach. Do not administer cathartics since they tend to promote loss of fluid and electrolytes. Treatment is generally supportive. Monitor serum electrolyte and renal function. Replacement of fluid and electrolytes may be indicated. Measures may be required to maintain respiratory, cardiovascular and renal function. Gastrointestinal irritation is usually of short duration but may be treated symptomatically.
The degree to which HCTZ is removed by hemodialysis has not been established.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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

AVAILABILITY
Hydrochlorothiazide (Hytaz®) 12.5 mg film-coated tablet, in flex foil strip x 10's (box of 200's)
Hydrochlorothiazide (Hytaz®) 25 mg film-coated tablet, in flex foil strip x 10's (box of 200's)

STORAGE CONDITION
Store at temperatures not exceeding 30°C
Keep the product out of sight and reach of children

Date of First Authorization: December 2005
Date of Revision of Package Insert: November 2008

REGISTRATION NUMBERS
Hytaz® 12.5 mg film-coated tablet – DR-XY30440
Hytaz® 25 mg film-coated tablet – DR-XY30255

Manufactured by **AMHERST LABORATORIES, INC.**
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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