Norplus®
10 mg/12.5 mg Tablet
angiotensin converting enzyme inhibitor / diuretic / antihypertensive

FORMULATION
Each tablet contains:
- Imidapril hydrochloride ........................................... 10 mg
- Hydrochlorothiazide ................................................ 12.5 mg

PRODUCT DESCRIPTION
Pink, round, biconvex film-coated tablet, 9/32" in diameter, plain on both sides

CLINICAL PHARMACOLOGY
Pharmacodynamics
Imidapril Hydrochloride
Imidapril is an ester prodrug which is hydrolyzed after oral administration to form the active angiotensin-converting enzyme (ACE) inhibitor imidaprilat. Imidaprilat has potent ACE inhibitory effects, 1.2 times and 2.6 times that of enalaprilat and captopril, respectively.

Imidapril’s blood pressure lowering effect is mainly due to ACE inhibition and consequent reduction in angiotensin II, resulting in dilatation of peripheral vessels and reduction in vascular resistance. The blood pressure lowering effect of imidapril is comparable to enalapril and five to ten times more potent than that of captopril.

Imidapril decreases total peripheral vascular resistance without an increase in heart rate or cardiac contractility. Imidapril increases renal blood flow and reduces renal vascular resistance mainly due to dilatation of the efferent arteriole. Imidapril showed no specific effect on the central nervous, digestive, respiratory, smooth muscle, reproductive, urologic, hematologic, and metabolic systems.

Hydrochlorothiazide
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 the 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.

Diuresis begins with two hours, peaks in about four hours and lasts about 6 to 12 hours after oral administration of HCTZ.

Pharmacokinetics
Imidapril Hydrochloride
About 70% of imidapril is absorbed from the gastrointestinal tract and reaches peak plasma concentration within 2 hours after oral administration. Plasma imidapril concentrations decline monophasically with a half-life of about 2 hours. A fat-rich meal significantly decreases imidapril absorption.
Imidapril undergoes de-esterification in the liver to form imidaprilat. Peak plasma imidaprilat concentrations are reached within 7 hours, and decline biphasically with an initial half-life of 7 to 9 hours and a terminal half life of more than 24 hours. The absolute bioavailability of imidaprilat is 42%. After multiple dosing, steady state imidaprilat concentrations are reached after 5 days. Protein binding of imidapril and imidaprilat is 85 and 53%, respectively.

After single oral dosing, imidapril absorption appeared linear with doses of 10 to 240 mg based on plasma and urinary excretion data. Drug elimination is primarily via renal (40%) and hepatobiliary (50%) routes.

The experience in all grades of renal impairment is limited. Increased plasma levels and area under the curve (AUC) of imidapril and imidaprilat were reported in patients with renal impairment. There was a two-fold increase in the AUC of imidaprilat in patients with creatinine clearance 30 to 80 mL/min and an almost tenfold increase in patients with creatinine clearance 10 to 29 mL/min.

In patients with hepatic impairment, the AUC of imidapril and imidaprilat were slightly higher than in normal subjects while the time to peak plasma concentration (T_{max}) for both was similar in the two groups. The half-life of imidaprilat, but not that of imidapril, was significantly increased in patients with hepatic impairment.

**Hydrochlorothiazide**

HCTZ is well absorbed from the gastrointestinal tract. Oral bioavailability is approximately 65 to 75%. After oral administration of HCTZ at doses of 12.5 to 100 mg, peak plasma concentrations of 70 to 490 ng/mL are observed within 1 to 5 hours of dosing.

Approximately 40 to 60% of the drug is bound to plasma proteins. HCTZ 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 an oral dose is eliminated unchanged within 24 hours. Increased HCTZ plasma concentrations and prolonged elimination half-life have been reported in patients with renal impairment.

**INDICATION**

Treatment of hypertension

**DOSAGE AND ADMINISTRATION**

Individualize dosage according to patient’s clinical response.

**Initial Adult Dose:** Orally, 1 tablet once daily.

**CONTRAINDICATIONS**

- Hypersensitivity to imidapril, any ACE inhibitor, HCTZ, other sulfonamide derivatives, or any component of the product
- History of angioneurotic edema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Pregnancy
- Breastfeeding
- Renovascular hypertension
- Renal failure with or without hemodialysis
- Anuria

**WARNINGS AND PRECAUTIONS**

ACE inhibitors (e.g., imidapril) can cause injury and even death to the developing fetus when used in pregnancy during the second and third trimesters. Discontinue imidapril as soon as possible upon detection of pregnancy.
Imidapril Hydrochloride

**Fetal/Neonatal Morbidity and Mortality:** ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors 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 observed, although it is not clear whether these occurrences were due to exposure to ACE inhibitors.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Discontinue imidapril as soon as possible when pregnancy is detected.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely monitored 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 a means of reversing hypotension and/or substituting for disordered renal function. Imidapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

**Hypotension:** Imidapril, like other ACE inhibitors, may cause a profound fall in blood pressure particularly after the first dose. Symptomatic hypotension is rarely observed in patients with uncomplicated hypertension. Hypotension is more likely if the patient has been volume-depleted (e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting) in hypertensive patients given imidapril. Symptomatic hypotension has also been observed in patients with heart failure (with or without associated renal insufficiency). This is most likely to occur in patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In these patients, treatment should be under medical supervision and patients should be monitored whenever the dose of imidapril and/or diuretic is adjusted. Apply similar considerations to patients with ischemic heart disease or cerebrovascular disease in whom an excessive fall in blood pressure may result in myocardial infarction or cerebrovascular accident.

If hypotension develops, place the patient in a supine position. Volume repletion with intravenous normal saline may be required. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with imidapril after effective management.

**Renovascular Hypertension:** There are no data available on the use of imidapril in patients with renovascular hypertension. An increased risk of severe hypotension and renal impairment has been observed in patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. Treatment of these patients should be under medical supervision, with low doses, careful titration, and monitoring of renal function.

**Renal Impairment:** Changes in renal function may be anticipated in susceptible individuals due to inhibition of the renin-angiotensin-aldosterone system. Thus, imidapril should be used with caution in patients with impaired renal function. Reduced doses are required for patients with creatinine clearance between 30 to 80 mL/min. Due to limited data, imidapril should not be given to patients with creatinine clearance <30 mL/min. Close monitoring of renal function during treatment should be performed.

Renal failure associated with ACE inhibitors has been reported and mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. Some patients, with no apparent pre-existing renal disease, have developed minor and usually transient elevations in blood urea and serum
creatinine when imidapril was coadministered with a diuretic. Reduction in imidapril dosage and/or discontinuation of the diuretic may be necessary. This situation should raise the possibility of underlying renal artery stenosis.

**Hemodialysis:** Anaphylactoid reactions such as facial swelling, flushing, hypotension, and dyspnea have been seen in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Symptoms usually appear within a few minutes after beginning hemodialysis. Consider giving a different type of dialysis membrane or a different class of antihypertensive agent in these patients.

**Kidney Transplantation:** There is no data on the use of imidapril in patients with recent kidney transplantation.

**Psoriasis:** Imidapril, as with other ACE inhibitors, should be used with caution in patients with psoriasis.

**Angioneurotic edema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients receiving ACE inhibitors, including imidapril. Symptoms occur during the first weeks of treatment. In rare cases, however, severe angioedema may develop after long term imidapril treatment. In such cases, immediately discontinue imidapril and institute appropriate monitoring until complete and sustained resolution of symptoms has occurred.

Angioedema associated with laryngeal edema or tongue edema may be fatal. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, particularly those with a history of airway surgery. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) or slow intravenous epinephrine 1 mg/mL (observe dilution instructions) with control of blood pressure and ECG. The patient should be hospitalized and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

**Hypersensitivity to Insect Toxins, Insect Bites:** When treated with an ACE inhibitor, patients with hypersensitivity to insect toxins who are undergoing desensitization treatment have an increased risk of severe anaphylactoid reactions. Discontinue imidapril before desensitization treatment. Similar reactions may occur after an insect bite in patients without known hypersensitivity to insect toxins.

**Anaphylactoid Reactions during LDL-Apheresis:** Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily discontinuing ACE inhibitor therapy prior to apheresis.

**Aortic Stenosis/Hypertrophic Cardiomyopathy:** Use with caution in patients with left ventricular valvular and outflow tract obstruction.

**Neutropenia/Agranulocytosis:** Neutropenia was rarely observed with imidapril. Neutropenia may occur in patients with some degree of renal impairment, particularly when it is associated with a collagen vascular disease, e.g., systemic lupus erythematosus, scleroderma, and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

**Cough:** Persistent nonproductive cough has been reported with all ACE inhibitors, presumably due to the inhibition of the degradation of endogenous bradykinin. Cough always resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

**Surgery/Anesthesia:** There are no data available on the use of imidapril under conditions of surgery or anesthesia. However, like other ACE inhibitors, imidapril may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anesthesia. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
Hyperkalemia: Hyperkalemia has been rarely reported in some patients receiving imidapril, particularly in the presence of renal insufficiency and/or cardiac failure. Risk factors for the development of hyperkalemia include:

- Renal insufficiency or worsening of renal function
- Age (>70 years old)
- Diabetes mellitus
- Intercurrent events (i.e., dehydration, acute decompensation, metabolic acidosis)
- Concomitant use of potassium salts, potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene) or potassium supplements or those patients taking other drugs associated with increases in serum potassium (e.g., heparin)

Hydrochlorothiazide

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.

Hepatic Impairment: Use with caution in patients with hepatic impairment or progressive liver disease since minor alternations of fluid and electrolyte balance may precipitate hepatic coma.

Renal Impairment: Use with caution in patients with severe renal impairment because thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with renal impairment.

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 Erythematous: 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. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

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. Thiazides have been reported to increase the urinary excretion of magnesium. This may result in hypomagnesemia.

INTERACTIONS WITH OTHER MEDICAMENTS

Imidapril Hydrochloride

**Potassium salts, Potassium-sparing diuretics, Potassium supplements:** May lead to significant increases in serum potassium. Use with caution and monitor serum potassium frequently if concomitant use is necessary due to hypokalemia.

**Diuretics:** Excessive blood pressure reduction. The possible hypotensive effect may be reduced by discontinuing the diuretic, increasing volume or salt intake prior to diuretic intake, and initiating therapy with a lower dose of imidapril.

**Antihypertensive agents:** Increased hypotensive effect of ACE inhibitors

**Lithium:** May decrease lithium excretion leading to lithium toxicity. Monitor serum lithium levels frequently.

**Anesthetic drugs:** May enhance the hypotensive effects of certain anesthetic drugs

**Narcotic drugs/Antipsychotics:** Postural hypotension may occur

**Allopurinol:** Data from other ACE inhibitors indicate an increased risk of leukopenia

**Cytostatic or Immunosuppressive agents, Systemic corticosteroids or Procaainamide:** May lead to an increased risk of leukopenia

**Nonsteroidal anti-inflammatory drugs (NSAIDs):** May reduce the antihypertensive effect of ACE inhibitors, increase serum potassium, and decrease renal function

**Rifampin:** May decrease the antihypertensive effect of imidapril

**Antidiabetics:** ACE inhibitors may enhance insulin sensitivity. As a consequence, symptomatic hypoglycemia may occur in patients concomitantly receiving insulin or oral antidiabetics and imidapril.

**Antacids:** May decrease imidapril bioavailability

**Sympathomimetics:** May decrease the antihypertensive effects of ACE inhibitors; patients should be carefully monitored to confirm that the desired effect is obtained.

**Alcohol:** May enhance the hypotensive effect of ACE inhibitors

**Hydrochlorothiazide**

**Alcohol, Barbiturates, or Narcotics:** Potentiation of orthostatic hypotension

**Amantadine:** Increased risk of adverse effects

**Aminoglycoside antibiotics:** Diuretic-induced volume depletion can potentiate aminoglycoside nephrotoxicity

**Anticholinergic agents (e.g., atropine, biperidine):** May increase availability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate.

**Antidiabetic drugs (oral agents and insulin):** Dosage adjustment of the antidiabetic drug may be necessary (see Warnings and Precautions, Metabolic and Endocrine Effects)

**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 myelosuppressive effects

**Pressor amines (e.g., epinephrine):** Possible decreased response to pressor amines but not sufficient to prevent their use

**Skeletal muscle relaxants, nondepolarizing (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.

**NSAIDs including COX-2 inhibitors:** May reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients

**Other antihypertensive drugs:** Additive effect

STATEMENT ON USAGE FOR HIGH RISK GROUPS
PREGNANCY: ACE inhibitors should not be used during pregnancy. When pregnancy is diagnosed, immediately discontinue treatment with ACE inhibitors, and, if appropriate, alternative treatment should be started (see Warnings and Precautions, Fetal/Neonatal Morbidity and Mortality).

LACTATION: Imidapril and thiazides appear in human milk. Discontinue breastfeeding or drug because of potential risk to breastfeeding infants, taking into consideration the importance of the drug to the mother.

GERIATRICS:

Imidapril Hydrochloride
Some elderly, particularly very old patients, may be more responsive to imidapril than younger patients.

Hydrochlorothiazide
Thiazide diuretics are more likely to cause hypovolemia, leading to orthostatic hypotension, and reduced glomerular filtration rate can occur. Elderly patients are also more prone to diuretic-induced hypokalemia due to poor dietary intake of potassium.

CHILDREN: The safety and efficacy in children have not been established.

UNDESIRABLE EFFECTS

Imidapril Hydrochloride
Cardiovascular: Severe hypotension after initiation of therapy or increase of dose; dizziness, feeling of weakness, impaired vision, and disturbance of consciousness (syncope) can also occur in association with hypotension; tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction, transient ischemic attacks, and cerebral hemorrhage

Gastrointestinal: Diarrhea, nausea, vomiting, gastritis, abdominal pain, constipation, dry mouth, cholestatic icterus, hepatitis, pancreatitis, ileus

Nervous: Occasionally, dizziness, weariness, fatigue, somnolence; rarely, depression, sleep disorders, paresthesias, impotence, disorder of balance, confusion, tinnitus, blurred vision, headache, taste disturbance

Renal: Renal insufficiency (rare), acute renal failure

Respiratory: Cough; rarely, dyspnea, sinusitis, rhinitis, glossitis, bronchitis, bronchospasm and angioedema involving the upper airways, and very rarely, allergic alveolitis/eosinophilic pneumonia

Skin: Occasionally, redness, itching, rash, urticaria, cases of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences, alopecia; cutaneous symptoms accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased antinuclear antibody (ANA) titers; onset of angioneurotic edema involving the face and oropharyngeal tissues

Other adverse effects: Increases in blood urea and plasma creatinine may occur, especially in the presence of renal insufficiency. This is reversible upon drug discontinuation. Elevation of serum potassium can occur since imidapril leads to decreased aldosterone secretion. Other reported adverse effects are decreases in hemoglobin, hematocrit, platelets, and white cell count as well as elevations of liver enzymes, serum bilirubin and creatine phosphokinase (CPK). Agranulocytosis or pancytopenia can also occur. Individual cases of hemolytic anemia in patients with congenital deficiency of G-6-PDH have been reported with other ACE inhibitors.

Hydrochlorothiazide

Body as a Whole: Fatigue, fever, weakness

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics, antihypertensive drugs), transient cerebral ischemic attacks

Gastrointestinal: Anorexia, constipation, cramping, diarrhea, gastric irritation, jaundice (intrahepatic cholestatic jaundice) nausea, pancreatitis, sialadenitis, spasms, stomach irritation, vomiting

Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, thrombocytopenia

Hypersensitivity Reactions: Anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, fever, photosensitivity, purpura, urticaria
**Metabolic and Nutritional:** Hyperglycemia, hyperuricemia, hypokalemia, hyponatremia, hypochloremic alkalosis, hypophosphatemia, hypomagnesemia, hypercalcemia, impairment of glucose tolerance, glycosuria; **Increases in the following:** total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides

**Musculoskeletal:** Muscle cramps, muscle spasm

**Nervous System:** Cephalalgia, dizziness, headache, impotence, insomnia, paresthesia, restlessness, vertigo

**Renal:** Renal impairment, renal failure, interstitial nephritis, renal dysfunction

**Skin:** Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, polyarteritis nodosa, alopecia

**Special senses:** Transient blurred vision, xanthopsia

**OVERDOSE AND TREATMENT**

**Imidapril Hydrochloride**
Symptoms of overdosage include severe hypotension, shock, stupor, bradycardia, electrolyte disturbances, and renal failure. After ingestion of an overdose, keep patient under close supervision, preferably in an intensive care unit. Monitor serum electrolytes and creatinine frequently. Measures to prevent absorption and hasten elimination such as gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes after intake should be applied if ingestion is recent.

If hypotension occurs, place patient in the shock position and immediately give salt and volume supplementation. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions may be treated with atropine. The use of a pacemaker may be considered.

Imidapril and imidaprilat may be removed from the circulation by hemodialysis. The use of high-flux polycrylonitrile membranes should be avoided.

**Hydrochlorothiazide**
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.

**STORE AT TEMPERATURES NOT EXCEEDING 30°C**

**KEEP OUT OF SIGHT AND REACH OF CHILDREN**

**AVAILABILITY**

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