DIURIL® (chlorothiazide) Oral Suspension

**DESCRIPTION**

DIURIL® (chlorothiazide) is a diuretic and antihypertensive. It is 6-chloro-2H-1,2,4-benzoazinidazole-7-sulfonamide-1,1-dioxide. Its empirical formula is C19H17ClN2O5S and its structural formula is:

![Structural formula of chlorothiazide]

It is a white, or practically white, crystalline powder with a molecular weight of 295.72, which is very slightly soluble in water, but readily soluble in dilute aqueous sodium hydroxide. It is soluble in urine to the extent of about 150 mg per 160 ml at pH 7.

DIURIL Oral Suspension contains 250 mg of chlorothiazide per 5 ml, alcohol 0.4%, with methylparaben 0.1%, propylparaben 0.02%, and benzoic acid 0.1% added as preservatives. The inactive ingredients are D&C Yellow 10, flavors, glycerin, purified water, sodium saccharin, sacrose and tragacanth.

**CLINICAL PHARMACOLOGY**

The mechanism of the antihypertensive effect of thiazides is unknown. DIURIL does not usually affect normal blood pressure. DIURIL affects the distal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy. DIURIL increases excretion of sodium and chloride in approximately equivalent amounts.

**INDICATIONS AND USAGE**

DIURIL is indicated in the management of hypertension either as the sole therapeutic agent or as an adjunctive therapy in edema associated with congestive heart failure, dehydration, cirrhosis of the liver, nephrosis, and albuminuria.

DIURIL has also been found useful in edema due to various forms of renal dysfunction such as diabetes, edema due to atherosclerotic heart disease, and edema due to liver cirrhosis, nephrosis, and electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia.

**CONTRAINDICATIONS**

Anuria.

Hypersensitivity to this product or to other sulfonamide-derived drugs.

**WARNINGS**

Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics (see PRECAUTIONS, Drug Interactions).

**PRECAUTIONS**

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalances, namely, hypokalemia, hypochloremia, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, numbness, paresthesia, tetany, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmias and also may also sensitize or exaggerate the response of the heart to the toxic effects of digoxin (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium-sparing diuretics or potassium supplements such as foods with a high potassium content.

Although diuretic effects are generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetics, doses adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may be manifested during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

**Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine)** - possible increased responsiveness to the muscle relaxant.

**Lithium** - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations for use before of such preparations with DIURIL.

**Non-steroidal Anti-inflammatory Drugs (NSAIDs) including Selective Cyclooxygenase-2 (COX-2) Inhibitors** - in some patients, the administration of a non-steroidal anti-inflammatory agent including a selective COX-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when DIURIL and non-steroidal anti-inflammatory agents or selective COX-2 inhibitors are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

**Drug/Laboratory Test Interactions**

Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS, General). Carcinogenesis, Mutagenesis, Impairment of Fertility

Chlorothiazide was not mutagenic in vitro in the Ames microbial mutagen test (using a maximum concentration of 5 mg/plate and Salmonella typhimurium strains TA98 and TA100) and was not mutagenic and did not induce mitotic nondisjunction in diploid strains of Aspergillus nidulans.

Chlorothiazide had no adverse effects on fertility in female rats at doses up to 60 mg/kg/day and no adverse effects on fertility in male rats at doses up to 40 mg/kg/day. These doses are 1.5 and 1 times the recommended maximum human dose, respectively, when compared on a body weight basis.

**Pregnancy**

Teratogenic Effects - Although reproduction studies performed with chlorothiazide doses of 50 mg/kg/day in rabbits, 60 mg/kg/day in rats and 500 mg/kg/day in mice revealed no external abnormalities of the fetus or impairment of growth and survival of the fetus due to thiazide exposure, such studies did not include complete examinations for visceral and skeletal abnormalities. It is not known whether chlorothiazide can cause fetal harm when administered to a pregnant woman; however, thiazides cross the placental barrier and appear in cord blood. DIURIL should be used during pregnancy only if clearly needed (see INDICATIONS AND USAGE).

**Nonteratogenic Effects - Chlorothiazide** may cause fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

**Nursing Mothers**

Because of the potential for serious adverse reactions in nursing infants from DIURIL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

There are no well-controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients (see DOSAGE AND ADMINISTRATION, Infants and children).

**Geriatric Use**

Clinical studies of DIURIL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see WARNINGS).

**ADVERSE REACTIONS**

The following adverse reactions have been reported and, within each category, are listed in order of decreasing frequency.

Body as a Whole:

- possible increased responsiveness to the muscle relaxant.
Cardiovascular: Hypotension, including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS).

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

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which chlorothiazide sodium is removed by hemodialysis has not been established.

The oral LD₅₀ of chlorothiazide is 8.5 g/kg, greater than 10 g/kg, and greater than 1 g/kg, in the mouse, rat and dog, respectively.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

Adults

For Edema

The usual adult dosage is 500 mg to 1,000 mg (10 mL to 20 mL) once or twice a day. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or on three to five days each week. With an intermittent schedule, excessive response and the resulting undesirable electrolyte imbalance are less likely to occur.

For Control of Hypertension

The usual adult starting dosage is 500 mg or 1,000 mg (10 mL to 20 mL) a day as a single or divided dose. Dosage is increased or decreased according to blood pressure response. Rarely some patients may require up to 2,000 mg (40 mL) a day in divided doses.

Infants and Children

For Diuresis and For Control of Hypertension

The usual pediatric dosage is 5 mg to 10 mg per pound (10 mg/kg to 20 mg/kg) per day in single or two divided doses, not to exceed 375 mg per day (7.5 mL or ½ to 1½ teaspoonsful of the oral suspension daily) in infants up to 2 years of age or 1,000 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 15 mg per pound (30 mg/kg) per day in two divided doses may be required (see PRECAUTIONS, Pediatric Use).

HOW SUPPLIED

DIURIL® (chlorothiazide) Oral Suspension, 250 mg of chlorothiazide per 5 mL, is a yellow, syrupy liquid, and is supplied as follows:

NDC 65649-311-12 250 mg per 5 mL 237 mL

Storage

DIURIL (chlorothiazide) Oral Suspension: Keep container tightly closed. Protect from freezing, –20°C (–4°F) and store at room temperature, 15° to 30°C (59° to 86°F).