**DIURIL®**  
**Chlorothiazide** Oral Suspension

**DESCRIPTION**  
DIURIL® (Chlorothiazide) is a diuretic and antihypertensive. It is 6-chloro-2H 1,2,4-benzothiadiazine-7-sulfonamide, 1,1-dioxide. Its empirical formula is C₇H₆ClN₃O₄S₂ and its structural formula is as follows:

\[
\text{NH}_2\text{SO}_3\text{Cl}\text{CH}_3\text{CH}₂\text{CH}_2\text{SO}_3\text{H}
\]

**DIURIL** is a white, or practically white, crystalline powder with a molecular weight of 295.72, which is soluble in water but not soluble in dilute aqueous sodium hydroxide. It is soluble in water to the extent of about 150 mg per 1 ml at pH 7.

**DIURIL Oral Suspension contains 250 mg of chlorothiazide per 5 ml, alcohol 0.5 percent, with methylparaben 0.12 percent, propylparaben 0.02 percent, and benzoic acid 0.1 percent added as preservatives. The inactive ingredients are D&C Yellow 10, flavors, glycérin, purified water, sodium saccharin, sucrose 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 renal 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.

DIURIL prolongs the effects of corticosteroids, ACTH, and anticoagulants.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

**Pharmacokinetics and Metabolism**

DIURIL is not metabolized but is eliminated rapidly by the kidney. The plasma half-life of chlorothiazide is 45-120 minutes. After oral doses, 10-15 percent of the dose is excreted unchanged in the urine. Chlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

**INDICATIONS AND USAGE**

DIURIL is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and congestion and edema.

DIURIL has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

DIURIL is indicated in the management of hypertension as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Use in Pregnancy
Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy. Because there is no satisfactory evidence that they are useful in the treatment of toxemia, Edema during pregnancy may arise from pathologic causes or may be related to the physiologic and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (see PRECAUTIONS).

Normal pregnancy, carrying the added burden of the normal pregnancy, there is no satisfactory evidence that they are useful in the treatment of toxemia of pregnancy. Therefore, during normal pregnancy there is hydrothorax which is not harmful to the fetus or the mother in the absence of cardiovascular disease. However the condition may be associated with extreme, rarely generalized edema, sex effeminate diseases which are increased in the post partum period. Therefore, when diuretics are used during pregnancy, they should be discontinued before carrying out tests for parity hormone. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight hypercalcemia, despite the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidenced by hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parity hormone.

The antihypertensive effect of the drug may be enhanced in the post-sympathectomy patient. Thiazides have been shown to increase the excretion of magnesium in this population.

**DIURIL** is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension. Use in Pregnancy.

Thiazides may potentiate the hypotensive effects of other antihypertensive drugs, e.g., beta blockers or ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

**Drug/Laboratory Test Interactions**

Thiazides should be discontinued before carrying out tests for parity hormone (see PRECAUTIONS).

**CONTRAINDICATIONS**

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

**WARNINGS**

Use 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 with caution in patients with impaired hepatic function or progressive liver disease. Because thiazides are capable of precipitating hepatic coma in patients with cirrhosis, 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 imbalance: namely, hypokalemia, hypochloremia, alkalosis, and hypokalemia.Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral alimentation. Diuretics may increase sodium loss and thus induce hypokalemia, irrespective of cause, include diuretics of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, euphoria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cramps is present or is prior to oliguria therapy. The differentiation between the signs of fluid or electrolyte deficit and the signs of acute potassium deficiency may be difficult and the signs and symptoms of both conditions may be present simultaneously.

Hypokalemia is usually reversible, but in the presence of moderate to severe liver disease, hypokalemia may be responsible for the development of hypomagnesemia.

**Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia.**

The combination should be administered with caution, especially in the elderly.

**Drug/Laboratory Test Interactions**

Thiazides should be discontinued before carrying out tests for parity hormone (see PRECAUTIONS).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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 time(s)* the recommended maximum human dose, respectively, when compared on a body weight basis.

**Pregnancy**

**Teratogenic Effects** - Pregnancy Category C

Although reproduction studies performed with chlorothiazide doses of 5 mg/kg/day in rabbits, 60 mg/kg/day in rats and 500 mg/kg/day in mice revealed no evidence of fetal defects or changes in the peri- or postnatal development of the fetus, due to chlorothiazide, 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).

**Antagonistic 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).

**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 elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low 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 severity:

**Body as a Whole**

- Weakness

- Weight increased

**Cardiovascular**

- Arrhythmia

**Dermatologic**

- Rash, pruritus

**Eyes**

- Blurred vision

**Gastrointestinal**

- Abdominal pain, cramps

**Genitourinary**

- Decreased libido, impotence

**Hematologic**

- Anemia, leukopenia

**Musculoskeletal**

- Arthralgia, myalgia

**Respiratory**

- Cough, pharyngitis

- Rhinorrhea

- Sinusitis

**Special Senses**

- Tinnitus

- Urinary retention

- Visual disturbances

**Systemic**

- Fever, chills

- Infection

- Liver function test abnormal

**Skeletal muscle reactivity, myalgia/pain, paresthesia - 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. Reference to the package insert for lithium preparations before use of such preparations with DIURIL.

Non-steroidal Anti-inflammatory Drugs 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 diuretics 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.

In some patients, the administration of NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors therefore may result in further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.
Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice, diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia. (See PRECAUTIONS, Metabolic: Electrolyte imbalance)

Hypersensitivity: Anaphylactic reactions, respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, 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.

OVERDOSAGE
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 1000 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 1000 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 2000 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 (2.5 mL to 7.5 mL, or ½ to 1½ teaspoonfuls of the oral suspension daily) in infants up to 2 years of age or 1000 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 Oral Suspension, 250 mg of chlorothiazide per 5 mL, is a yellow, creamy suspension, and is supplied as follows: NDC 66649-311-12, bottles of 237 mL.

Storage
DIURIL 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).