Chlorothiazide Sodium for Injection, USP

FOR THE PREPARATION OF INTRAVENOUS SOLUTION

Rx only

DESCRIPTION
Chlorothiazide Sodium for Injection, USP is a diuretic and antihypertensive. It is 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide monosodium salt and its molecular weight is 317.71. Its empirical formula is C_{5}H_{5}ClINaO_{4}S_{2} and its structural formula is:

![Chemical Structure of Chlorothiazide Sodium](image)

Chlorothiazide Sodium for Injection, USP is a sterile lyophilized white powder and is supplied in a vial containing:

- Chlorothiazide sodium equivalent to chlorothiazide ........................................ 500 mg
- Mannitol .................................................................................................................. 250 mg
- Sodium hydroxide to adjust pH.

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![Chemical Structure of Chlorothiazide](image)

It is a white, or practically white, crystalline powder with a molecular weight of 395.72, 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 100 mL at pH 7.

CLINICAL PHARMACOLOGY
The mechanism of the antihypertensive effect of thiazides is unknown. Chlorothiazide does not usually affect normal blood pressure.

Chlorothiazide affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy. Chlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts.

Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. Following intravenous use of Chlorothiazide Sodium, onset of the diuretic action occurs in 15 minutes and the maximal action in 30 minutes.

Pharmacokinetics and Metabolism
Chlorothiazide is not metabolized but is eliminated rapidly by the kidney; 96 percent of an intravenous dose is excreted unchanged in the urine within 23 hours. The plasma half-life of chlorothiazide is 45 to 120 minutes. Chlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE
Chlorothiazide Sodium for Injection is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy. Chlorothiazide Sodium for Injection has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

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 and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Edema during pregnancy may arise from pathologic causes or from 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, Pregnancy). Dependent edema in pregnancy, resulting from restriction of venous return by the gravid uterus, is properly treated through elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in this instance is illogical and may be dangerous. Although any chloride deficit is 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.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Hyperkalemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postpartum hypertensive patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing 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 elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Laboratory Tests
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Drug Interactions
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 - additive effect or potentiation.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.

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 before use of such preparations with chlorothiazide sodium.

Non-steroidal Anti-inflammatory Drugs - in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when Chlorothiazide Sodium and non-steroidal anti-inflammatory agents 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).

PRECAUTIONS
General
All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, 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, muscular fatigue, 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.

Hypokalemia may cause cardiac arrhythmias and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (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 any chloride deficit is 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.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

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 with caution 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.

Lithium generally should not be given with diuretics (see PRECAUTIONS, Drug Interactions).

Use in Children
Anuria.

Hypersensitivity to any component of this product or to other sulfonamide-derived drugs.

WARNINGS
Intravenous use in infants and children has been limited and is not generally recommended.
Although reproduction studies performed with chlorothiazide sodium in rats revealed no evidence of impaired fertility due to the compound, no adequate and well-controlled studies in pregnant women have been conducted with chlorothiazide sodium. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see Pregnancy).

Chlorothiazide sodium is not known to produce an increased risk of birth defects when administered to pregnant women. However, hypokalemia, hyponatremia, and dehydration resulting from excessive diuresis may cause fetal distress when they are severe (see Precautions).

Teratogenic Effects - Pregnancy Category C: Although reproduction studies performed with chlorothiazide sodium 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 or survival of the fetus due to chlorothiazide, such studies did not include complete examinations for visceral and skeletal abnormalities. It is not known whether chlorothiazide sodium can cause fetal harm when administered to a pregnant woman; however, thiazides cross the placental barrier and appear in cord blood. Chlorothiazide should be used during pregnancy only if clearly needed (see INDICATIONS AND USAGE).

Teratogenic 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 Chlorothiazide Sodium for Injection, 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
Safety and effectiveness of Chlorothiazide Sodium for Injection in pediatric patients have not been established.

Geriatric Use
Clinical studies of Chlorothiazide Sodium for Injection 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 based on the same principles that guide selection of therapy in other age groups. Dosages of 25 mg or less may be suitable for many elderly patients. In addition, 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.
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 angitis (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.
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.
Special Senses: Transient blurred vision, xanthish.
Renal: Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); hematuria (following intravenous use).
Urogenital: Impotence.

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

To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc. at 1-800-932-5676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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. 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 intravenous LD50 of chlorothiazide in the mouse is 1.1 g/kg.