Hydrochlorothiazide tablets are indicated in the management of various forms of renal dysfunction such as nephrotic syndrome, acute glucosuric nephropathy, and chronic renal failure. It is also indicated as adjunctive therapy in congestive heart failure, hepatic cirrhosis, and congestive heart failure due to pathologic causes. Hydrochlorothiazide is not metabolized and is excreted unchanged in the urine within 24 hours. About 61% of the oral dose is eliminated unchanged within 24 hours. It is not dialyzable, and it is not excreted in breast milk.

**INDICATIONS AND USAGE**

Hydrochlorothiazide tablets are used in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy. Hydrochlorothiazide tablets have also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glucosuric nephropathy, and chronic renal failure. Hydrochlorothiazide tablets are not metabolized and are excreted unchanged in the urine within 24 hours. It is not dialyzable, and it is not excreted in breast milk.

**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. Chlorothiazide is contraindicated in patients with impaired renal function. Thiuram derivatives may cause an idiopathic allergic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. Clinical laboratory examinations should be performed to detect metabolic alkalosis and hyperuricemia.

**DIAGNOSTIC TESTS**

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretics. Laboratory tests should be performed to detect metabolic alkalosis and hyperuricemia.

**PRECAUTIONS, Drug Interactions**

Hydrochlorothiazide itself has been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiouracil may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evident with thiazide diuretics. Thiauracil should be discontinued before carrying out tests for parathyroid function.

**LABORATORY TESTS**

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals. When given concurrently, the following drugs may interact with thiazide diuretics.

**Drug Interactions**

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.

**ADVERSE REACTIONS**

- Diuresis: Increased responsiveness to the muscle relaxant.
- Hypokalemia: 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).

**ACUTE MYOPA and SECONDARY ANGLE-CLOSURE GLAUCOMA**

Hydrochlorothiazide, a sulfonamide, causes an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

**PRECAUTIONS, General**

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hypokalemia, 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. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. 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. Dilutional hypokalemia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hypokalemia 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 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 therapy.

The antihypertensive effect of the drug may be enhanced in the post-sympathetic hyper-reactent 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. Thiouracil may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evident with thiazide diuretics. Thiouracil should be discontinued before carrying out tests for parathyroid function.

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

**ADVERSE REACTIONS**

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).

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The antihypertensive effect of the drug may be enhanced in the post-sympathetic hyper-reactent 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. Thiouracil may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evident with thiazide diuretics. Thiouracil should be discontinued before carrying out tests for parathyroid function.

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

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 hydrochlorothiazide 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).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic in vitro or in the Ames mutagenicity assay of Salmoneella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosome, and the L5178Y/mi tk- reversion test in vivo (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy
Teratogenic Effects, Prenatal Category B
Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nontransglutaminase-Dependent
Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers
Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, 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, IGN, Infants and Children).

ADVERSE REACTIONS
The following adverse reactions have been reported and, within each category, are listed in order of decreasing severity. Listed are adverse effects that may occur with the use of this drug according to body system. The frequency of occurrence is based on spontaneous post-marketing reports submitted to the FDA and the manufacturer and is not a complete enumeration of all possible adverse reactions.

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

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

Hematology: Agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

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

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

Musculoskeletal: Muscle spasm.

Neuromuscular and psychological: 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.

Sensory: Transient blurred vision, xanthenes.

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 (hyponatremia, hypochloremia, hypocalcemia) 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 hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

DOSEAGE 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 25 mg to 100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or on 3 to 5 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 initial dose in adults is 25 mg daily given as a single or two divided doses. Doses above 50 mg are often associated with marked reductions in serum potassium (see also PRECAUTIONS).

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

Infants and Children
For Diuretic and for Control of Hypertension
The usual pediatric dosage is 0.5 mg to 1 mg per pound (1 to 2 mg/kg) per day in single or two divided doses, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required (see PRECAUTIONS, Pediatric Use).

HOW SUPPLIED
Hydrochlorothiazide Tablets, USP 25 mg, are peach-colored, round, scored tablets debossed “3571” and “V” on one side.

They are supplied as follows:

- Tablets of 10: NDC 0603-3856-10
- Tablets of 30: NDC 0603-3856-16
- Tablets of 50: NDC 0603-3856-19
- Tablets of 100: NDC 0603-3856-21
- Tablets of 500: NDC 0603-3856-28
- Tablets of 1000: NDC 0603-3856-32
- Tablets of 5000: NDC 0603-3856-34

Hydrochlorothiazide Tablets, USP 50 mg, are peach-colored, round, scored tablets debossed “3572” and “V” on one side.

They are supplied as follows:

- Tablets of 10: NDC 0603-3857-10
- Tablets of 30: NDC 0603-3857-16
- Tablets of 50: NDC 0603-3857-19
- Tablets of 100: NDC 0603-3857-21
- Tablets of 500: NDC 0603-3857-28
- Tablets of 1000: NDC 0603-3857-32

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Manufactured for:
QUALTEST PHARMACEUTICALS
Huntsville, AL 35811

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