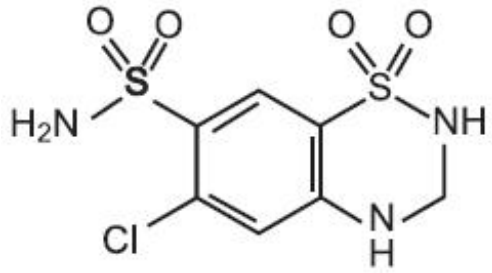
HYDROCHLOROTHIAZIDE- hydrochlorothiazide capsule
Preferred Pharmaceuticals Inc.

Hydrochlorothiazide Capsules USP

Rx only

DESCRIPTION

Hydrochloro-thiazide is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$; its molecular weight is 297.74; and its structural formula is:



It is a white, or practically white, crystalline powder which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Hydrochloro-thiazide is supplied as 12.5 mg capsules for oral use. Each capsule contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, and magnesium stearate. The hard gelatin shell consists of gelatin, titanium dioxide, sodium lauryl sulphate, FD&C Blue #1, D&C Red #28, D&C Yellow #10, black iron oxide and shellac.

CLINICAL PHARMACOLOGY

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodi-um traversing the distal tubule and the volume of water excret-ed. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydro-chlorothiazide and depletion of sodium, compensatory mecha-nisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions.

Hydrochlorothiazide also decreases the excretion of cal-cium and uric acid, may increase the excretion of iodide and may reduce glomerular fil-tration rate. Metabolic toxicities associated with excessive elec-trolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

Pharmacokinetics and Metabolism:

Hydrochlorothiazide is well absorbed (65% to 75%) fol-lowing oral administration. Absorption of hydrochlorothi-azide is reduced in patients with congestive heart failure.

Peak plasma concentrations are observed within 1 to 5 hours of dosing and range from 70 to 490 ng/mL follow-ing oral doses of 12.5 to 100 mg. Plasma concentra-tions are linearly related to the administered dose. Concen-trations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approxi-mately 40% to 68%. The plas-ma elimination half-life has been reported to be 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma con-centrations of hydrochlorothi-azide are increased and the elimination half-life is pro-longed.

When hydrochloro-thiazide is adminis-tered with food, its bioavailabil-ity is reduced by 10%, the max-imum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6 to 2.9 hours.

Pharmacodynamics:

Acute antihypertensive effects of thi-azides are thought to result from a reduction in blood vol-ume and cardiac output, sec-ondary to a natriuretic effect, although a direct vasodilatory mechanism has also been pro-posed. With chronic adminis-tration, plasma volume returns toward normal, but peripheral vascular resistance is de-creased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Thiazides do not affect normal blood pressure. Onset of action occurs within 2 hours of dos-ing, peak effect is observed at about 4 hours, and activity per-sists for up to 24 hours.

Clinical Studies:

In an 87 patient 4-week double-blind, placebo controlled, parallel group trial, patients who received hydrochloro-thiazide had reductions in seated systolic and diastolic blood pressure that were significantly greater than those seen in patients who received placebo. In published placebo-controlled trials com-paring 12.5 mg of hydrochlorothiazide to 25 mg, the 12.5 mg dose preserved most of the placebo-corrected blood pressure reduction seen with 25 mg.

INDICATIONS AND USAGE

Hydrochloro-thiazide capsules are indicated in the management of hypertension either as the sole therapeutic agent, or in combination with other antihypertensives. Unlike potassium sparing combina-tion diuretic products, hydrochloro-thiazide capsules may be used in those patients in whom the development of hyperkalemia cannot be risked, including patients taking ACE inhibitors.

Usage in Pregnancy:

The rou-tine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unneces-sary hazard. Diuretics do not prevent

development of tox-emia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indi-cated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnan-cy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unneces-sary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular dis-ease), but which is associated with edema, including general-ized edema in the majority of pregnant women. If this edema produces discomfort, in-creased recumbency will often provide relief. In rare instances this edema may cause extreme discomfort which is not relieved by rest. In these cases a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

Hydrochlorothiazide capsules are con-traindicated in patients with anuria. Hypersensitivity to this product or other sulfonamide derived drugs is also con-traindicated.

WARNINGS

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause 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.

Diabetes and Hypoglycemia: Latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.

Renal Disease: Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia.

PRECAUTIONS

Electrolyte and Fluid Balance Status: In published studies, clinically significant hypokalemia has been consistently less common in patients who received 12.5 mg of hydro-chlorothiazide than in patients who received higher doses. Nevertheless, periodic determi-nation of serum electrolytes should be performed in patients who may be at risk for the development of hypo-kalemia. Patients should be observed for signs of fluid or electrolyte disturbances, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia and hypomagnesemia.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, mus-cular fatigue, hypotension, oliguria, tachycardia, and gas-trointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is pres-ent, during concomitant use of corticosteroid or adrenocorti-cotropic hormone (ACTH) or after prolonged therapy. Interference with adequate oral electrolyte intake will also con-tribute to hypokalemia. Hypo-kalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of dig-italis. Hypokalemia may be avoided or treated by potas-sium supplementation or increased intake of potassium rich foods.

Dilutional hyponatremia is life-threatening and may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hypo-natremia is life-threatening. In actual salt depletion, appropri-ate replacement is the therapy of choice.

Hyperuricemia: Hyperuricemia or acute gout may be precipi-tated in certain patients receiv-ing thiazide diuretics.

Impaired Hepatic Function: Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver dis-ease.

Parathyroid Disease: Calcium excretion is decreased by thi-azides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophos-phatemia, have been observed in a few patients on prolonged thiazide therapy.

Information for Patients:

Non-melanoma Skin Cancer: Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

Drug Interactions:

When given concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: potentiation of ortho-static 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.

Cholestyramine and colestipol resins: Cholestyramine and colestipol resins bind the hydrochlorothiazide and re-duce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroid, ACTH: intensi-fied 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 clear-ance of lithium and greatly increase the risk of lithium tox-icity. Refer to the package insert for lithium preparations before use of such preparations with hydrochloro-thiazide.

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. When hydrochloro-thiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patients 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 approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella 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 chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1,300 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: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3,000 and 1,000 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.

Nonteratogenic Effects: 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:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

A greater blood pressure reduction and an increase in side effects may be observed in the elderly (i.e., >65 years) with hydrochlorothiazide. Starting treatment with the lowest available dose of hydrochlorothiazide (12.5 mg) is therefore recommended. If further titration is required, 12.5 mg increments should be utilized.

ADVERSE REACTIONS

The adverse reactions associated with hydrochlorothiazide have been shown to be dose related. In controlled clinical trials, the adverse events reported with doses of 12.5 mg hydrochlorothiazide once daily were comparable to placebo. The following adverse reactions have been reported for doses of hydrochlorothiazide 25 mg and greater and, within each category, are listed in the 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 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, paresthesia, 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.

Postmarketing Experience:

The following adverse reaction has been identified during post-approval use of hydrochlorothiazide. Because the reaction is reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Non-melanoma Skin Cancer: Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000 mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

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 hydrochlorothiazide is removed by hemodialysis has not been established.

The oral LD_{50} of hydrochlorothiazide is greater than 10 gm/kg in the mouse and rat.

DOSAGE AND ADMINISTRATION

For Control of Hypertension: The adult initial dose of hydrochloro-thiazide is one capsule given once daily whether given alone or in combination with other antihypertensives. Total daily doses greater than 50 mg are not recommended.

HOW SUPPLIED

Hydrochlorothiazide Capsules USP 12.5 mg are blue/blue size ‘4’ hard gelatin capsules, imprinted with ‘D’ on blue cap and ‘26’ on blue body with black edible ink, filled with white to off-white powder.

Bottles of 7	NDC **68788-8862-7**
Bottles of 30	NDC **68788-8862-3**
Bottles of 60	NDC **68788-8862-6**

Bottles of 90 NDC **68788-8862-9**

Bottles of 100 NDC **68788-8862-1**

Dispense in a tight, light-resistant container as defined in the USP.

Keep out of reach of children.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light, moisture, freezing, -20°C (-4°F). Keep container tightly closed.

Distributed by:
Rising Pharma Holdings, Inc.
East Brunswick, NJ 08816

Made in India
Code: TS/DRUGS/19/1993

Revised: 09/2024

Repackaged By: Preferred Pharmaceuticals Inc.

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 12.5 mg

Rising® **NDC 68788-8862**
PHARMACEUTICALS

Hydrochlorothiazide
Capsules USP
12.5 mg

Rx only

Repackaged By: Preferred Pharmaceuticals Inc.

HYDROCHLOROTHIAZIDE

hydrochlorothiazide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68788-8863(NDC:57237-002)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)	HYDROCHLOROTHIAZIDE	12.5 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	BLUE	**Score**	no score
Shape	CAPSULE	**Size**	15mm

Flavor		**Imprint Code**	D;26
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68788-8863-7	7 in 1 BOTTLE; Type 0: Not a Combination Product	04/11/2025	
2	NDC:68788-8863-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/11/2025	
3	NDC:68788-8863-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	04/11/2025	
4	NDC:68788-8863-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/11/2025	
5	NDC:68788-8863-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/11/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078164	04/11/2025	

Labeler - Preferred Pharmaceuticals Inc. (791119022)

Registrant - Preferred Pharmaceuticals Inc. (791119022)

Establishment

Name	Address	ID/FEI	Business Operations
Preferred Pharmaceuticals Inc.		791119022	REPACK(68788-8863)

Revised: 4/2025 Preferred Pharmaceuticals Inc.