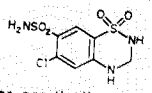
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:83972

PRINTED LABELING

HYDROCHLOROTHIAZIDE TABLETS

DESCRIPTION: Hydrochlorothiazide is a diuretic and antihypertensive. Hydrochlorothiazide 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 chemical structure is



Hydrochlorothiazide is a white, or practically white, crystalline powder slightly soluble in water, but freely soluble in Sodium Hydroxide Solution.

ACTIONS: The mechanism of action results in an interference with the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency. The mechanism whereby thiazides function in the control of hypertension is unknown.

INDICATIONS: Hydrochlorothiazide is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis and corticosteroid and estrogen therapy.

Hydrochlorothiazide has also been found useful in edema due to various forms of renal dysfunction as:

Nephrotic syndrome;
Acute glomerulonephritis; and
Chronic renal failure.

Hydrochlorothiazide is indicated in severe edema when due to pregnancy. (See "Contraindications" and "Warnings" below).

Diuretics are indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effect of other anti-hypertensive drugs in the more severe forms of hypertension and in the control of hypertension of pregnancy. The drug is also indicated in toxemia of pregnancy (eclampsia); angina due to congestive heart failure and/or hypertension; and "drug induced" edema.

CONTRAINDICATIONS: Anuria

Hypersensitivity to this or other sulfonamide derived drugs.

The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS: Should be used with caution in severe renal disease. In patients with renal disease, Hydrochlorothiazide may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alteration of fluid and electrolyte balance may precipitate hepatic coma.

Hydrochlorothiazide may be additive or potentiative of the action of other anti-hypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

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

USAGE IN PREGNANCY: Usage of Hydrochlorothiazide in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS: Hydrochlorothiazide crosses the placental barrier and appears in cord blood and breast milk.

PRECAUTIONS: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving Hydrochlorothiazide therapy should be observed for clinical signs 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. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: Dryness of mouth, thirst, weakness, letheargy. drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with Hydrochlorothiazide as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). 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 frank gout may be precipitated in certain patients receiving Hydrochlorothiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during Hydrochlorothiazide administration. Hydrochlorothiazide may increase the responsiveness to tubocurarine.

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

Hydrochlorothiazide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Hydrochlorothiazide may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS

A. Gastrointestinal System Reactions

1. anorexia
2. gastric irritation
3. nausea
4. vomiting
5. cramping
6. diarrhea
7. constipation
8. jaundice (intrahepatic cholestatic jaundice)
9. pancreatitis

B. Central Nervous System Reactions

1. dizziness
2. vertigo
3. parasthesias
4. headache
5. xanthopsia

C. Hematologic Reactions

1. leukopenia
2. agranulocytosis
3. thrombocytopenia
4. aplastic anemia

D. Dermatologic - Hypersensitivity Reactions

1. purpura
2. photosensitivity
3. rash
4. urticaria
5. necrotizing angiitis (vasculitis) (cutaneous vasculitis)

E. Cardiovascular Reaction

Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics.

F. Other

1. hyperglycemia
2. glycosuria
3. hyperuricemia
4. muscle spasm
5. weakness
6. restlessness

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

DOSAGE AND ADMINISTRATION: Therapy should be indiivdualized according to patient response. Use the smallest dosage necessary to achieve the required response.

ADULTS

For Diuresis: The usual adult dosage is 50 to 100 mg. 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.

In edema and toxemia of pregnancy, the recommended dosage is 100 mg. daily or, in severe cases and for brief periods, 200 mg. daily (in divided doses). Frequency of use may range from once every four days to daily.

For Control of Hypertension: The usual adult starting dose is 50 mg. twice daily. Dosage is increased or decreased according to the blood pressure response of the patient. Some patients may require 200 mg. daily in divided doses.

Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 per cent as soon as it is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of this agent, a further reduction in dosage, or even discontinuation of other antihypertensive drugs may be necessary.

INFANTS AND CHILDREN

The usual pediatric dosage is based on 1.0 mg. of Hydrochlorothiazide per pound of body weight per day in two doses. Infants under 6 months of age may require up to 1.5 mg. per pound per day in two doses.

On this basis, infants up to 2 years of age may be given 12.5 to 37.5 mg. daily in two doses. Children from 2 to 12 years of age may be given 37.5 to 100 mg. daily in two doses. Dosage in both age groups should be based on body weight.

HOW SUPPLIED: Each peach-colored scored tablet contains: Hydrochlorothiazide 25 mg. or 50 mg.

NDC 555-19-5
1000 TABLETS

Hydrochlorothiazide

TABLETS, U.S.P.

25mg.

Usual Dosage:
See package insert.

CAUTION:
Federal law
prohibits dispensing
without prescription.

BARR LABORATORIES, INC.
NORTHVALE, N.J. 07647

Lot No:

NDC 555-20-5
1000 TABLETS

Hydrochlorothiazide

TABLETS, U.S.P.

50mg.

Usual Dosage:
See package insert.

CAUTION:
Federal law
prohibits dispensing
without prescription.

BARR LABORATORIES, INC.
NORTHVALE, N.J. 07647

Lot No: