PHYSICIANS CIRCULAR

Tablets
MODURETIC®†
(hydrochlorothiazide and amiloride HCl, MSD)

MODURETIC (hydrochlorothiazide and amiloride HCl, MSD) is a diuretic/antihypertensive combining the potent natriuretic action of hydrochlorothiazide with the potassium-conserving property of amiloride HCl.

MODURETIC provides diuretic and antihypertensive activity (principally due to the hydrochlorothiazide component), while acting through the amiloride component to prevent the excessive potassium loss that may occur in patients receiving a thiazide diuretic. Due to its amiloride component, the urinary excretion of magnesium is less with MODURETIC than with a thiazide or loop diuretic used alone.

The mild diuretic and antihypertensive actions of amiloride HCl are additive to the natriuretic, diuretic and antihypertensive activity of the thiazide while minimizing the loss of potassium and bicarbonate and lessening the likelihood of acid-base imbalance.

The onset of the diuretic action of MODURETIC is within 2 hours and this action appears to be sustained for approximately 24 hours.

HYDROCHLOROTHIAZIDE

Hydrochlorothiazide is an orally effective diuretic and antihypertensive.

Onset of action following oral administration of hydrochlorothiazide occurs in 2 hours and reaches a peak effect in about 4 hours. The diuretic activity persists for approximately 6 to 12 hours. Hydrochlorothiazide does not affect normal blood pressure.

AMILORIDE HCl

Amiloride HCl is a potassium-conserving drug which possesses mild natriuretic, diuretic, and antihypertensive activity. The principal use is to conserve potassium in patient's receiving diuretic agents in whom excessive potassium losses occur or are expected.

Amiloride HCl usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours.

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† Registered Trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, USA

INDICATIONS

MODURETIC is indicated in patients in whom potassium depletion might be suspected or anticipated. MODURETIC, the combination of amiloride HCl and hydrochlorothiazide, minimizes the possibility of the development of excessive potassium loss in patients during vigorous diuresis for prolonged periods. MODURETIC, with the potassium sparing component amiloride HCl, is especially indicated in those conditions where the positive effect on potassium balance is particularly important.

MODURETIC may be used alone or as an adjunct to other antihypertensive drugs in conditions such as:

- Hypertension
- Edema of cardiac origin
- Hepatic cirrhosis with ascites and edema.

DOSAGE AND ADMINISTRATION

GENERAL DOSAGE CONSIDERATIONS

MODURETIC is available for oral use in one tablet strengths (see AVAILABILITY).

The following dosage refers to the administration of tablets.

HYPERTENSION

The usual dosage is one tablet of MODURETIC given once a day or in divided doses. Some patients may require only half a tablet MODURETIC once a day.

EDEMA OF CARDIAC ORIGIN

MODURETIC may be started at a dosage of one tablet a day. Dosage may be increased if necessary but must not exceed two tablets a day. The optimal dosage is determined by the diuretic response and the serum potassium level. Once an initial diuresis has been achieved, reduction in dosage should be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

HEPATIC CIRRHOSIS WITH ASCITES (see PRECAUTIONS)

Treatment should be initiated with a small dose of MODURETIC (1 tablet once a day). If necessary, dosage may be increased gradually until there is effective diuresis. The dosage should not exceed two tablets per day.

Maintenance doses may be lower than those required to initiate diuresis; therefore, reduction in the daily dose should be attempted when the patient's weight is stabilized. Gradual weight reduction in cirrhotic patients is especially desirable to reduce the likelihood of untoward reactions associated with diuretic therapy.

CONTRAINDICATIONS

- Hyperkalemia (defined as >5.5 mEq/l)
- Other concomitant antikaliuretic therapy or potassium supplementation (see PRECAUTIONS)
- Renal insufficiency (anuria, acute renal failure, severe progressive renal disease, and diabetic nephropathy; see also PRECAUTIONS)
- Hypersensitivity to any component of this product or other sulfonamide-derived drugs

PRECAUTIONS

HYPERKALEMIA

Hyperkalemia (serum potassium >5.5 mEq/l) has been observed in patients who received amiloride HCl either alone or concomitantly with other diuretic drugs. Hyperkalemia has been noted particularly in elderly patients and in hospitalized patients with hepatic cirrhosis or cardiac edema who have known renal involvement, are seriously ill, or are undergoing vigorous diuretic therapy. These patients should be monitored carefully for clinical, laboratory, and electrocardiographic (ECG) evidence of hyperkalemia. Some deaths have been reported in this group of patients.

Potassium supplementation in the form of medication or a potassium-rich diet should not be used with MODURETIC except in severe and/or refractory cases of hypokalemia. If potassium supplementation is used, careful monitoring of the serum potassium level is recommended.

TREATMENT OF HYPERKALEMIA

Should hyperkalemia occur in patients taking MODURETIC, the drug should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

IMPAIRED RENAL FUNCTION

When creatinine clearance falls below 30 ml/min thiazide diuretics are ineffective.

Patients with increases in blood urea nitrogen (BUN) over 30 mg per 100 ml, with serum creatinine levels over 1.5 mg per 100 ml, or with whole blood urea values over 60 mg per 100 ml, or with diabetes mellitus should not receive MODURETIC without careful, frequent monitoring of serum electrolytes and BUN levels. Potassium retention in the presence of renal impairment is accentuated by the addition of an antikaliuretic agent and may result in the rapid development of hyperkalemia.

ELECTROLYTE IMBALANCE

Although the likelihood of electrolyte imbalance is lessened with MODURETIC, careful check should be kept for signs of fluid and electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, hypokalemia and hypomagnesemia. It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, 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, after prolonged therapy or when severe cirrhosis is present. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Diuretic induced hyponatremia is usually mild and asymptomatic. In a few patients hyponatremia may become severe and symptomatic. Such patients require immediate attention and appropriate treatment.

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. Thiazides should be discontinued before carrying out tests for parathyroid function.

AZOTEMIA

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of renal disease, the diuretic should be discontinued.

HEPATIC DISEASE

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.

METABOLIC

Hyperuricemia may occur or gout may be precipitated in certain patients receiving thiazide therapy.

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

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

To minimize the risk of hyperkalemia in diabetic or suspected diabetic patients, the status of renal function should be known before initiating therapy with MODURETIC. Therapy with MODURETIC should be discontinued for at least three days prior to glucose tolerance testing.

Antikaliuretic therapy should be instituted only with caution in seriously ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease and patients with inadequately controlled diabetes. Shifts in acid-base balance alter the balance of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

SENSITIVITY REACTIONS

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

USE IN PREGNANCY

The routine use of diuretics in otherwise healthy pregnant women with or without mild edema is not recommended 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.

Thiazides cross the placental barrier and appear in cord blood. Therefore, the use of MODURETIC when pregnancy is present or suspected requires that the benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occurred in the adult.

NURSING MOTHERS

Thiazides appear in breast milk. If use of the drug is deemed essential, the patient should stop nursing.

PEDIATRIC USE

The use of amiloride HCl in children has not been established; therefore, MODURETIC is not recommended in the pediatric age group.

DRUG INTERACTIONS

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 inserts for lithium preparations before use of such preparations.

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 diuretics. Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride HCl, may cause hyperkalemia and renal failure, particularly in elderly patients. Therefore, when amiloride HCl is used concomitantly with NSAIDs, renal function and serum potassium levels should be carefully monitored.

Amiloride HCl

When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Hydrochlorothiazide

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. Diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with an ACE inhibitor to reduce the likelihood of first dose hypotension.

Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

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.

Drug/Laboratory Test Interactions - Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see PRECAUTIONS).

SIDE EFFECTS

MODURETIC is usually well tolerated. Although minor side effects have been reported relatively frequently, significant side effects have been reported infrequently.

Side effects that have been reported with MODURETIC are generally those known to be associated with diuresis, thiazide therapy, or with the underlying disease being treated. Clinical trials have not demonstrated that combining amiloride and hydrochlorothiazide increases the risk of adverse reactions over those seen with the individual components.

The following side effects have been reported with MODURETIC:

Body as a Whole
- headache*
- weakness*
- fatigue
- malaise
- chest pain
- back pain
- syncope

Cardiovascular
- arrhythmia
- tachycardia
- digitalis toxicity
- orthostatic hypotension
- angina pectoris

Digestive
- nausea/anorexia*
- vomiting
- diarrhea
- constipation
- abdominal pain
- GI bleeding
- appetite changes
- abdominal fullness
- flatulence
- thirst
- hiccups

Metabolic
- elevated serum potassium levels (>5.5 mEq per liter)
- electrolyte imbalance
- hyponatremia (see PRECAUTIONS)
- gout
- dehydration
- symptomatic hyponatremia

Integumentary
- rash*
- pruritus
- flushing
- diaphoresis

Musculoskeletal
- leg ache
- muscle cramps

joint pain

Nervous
- dizziness*
- vertigo
- paresthesia
- stupor

Psychiatric
- insomnia
- nervousness
- mental confusion
- depression
- sleepiness

Respiratory
- dyspnea

Special Senses
- bad taste
- visual disturbance
- nasal congestion

Urogenital
- impotence
- dysuria
- nocturia
- incontinence
- renal dysfunction including renal failure

OVERDOSAGE

No data are available with regard to overdosage in humans. The oral LD_{50} of the combination drug is 189 and 422 mg/kg for female mice and female rats, respectively.

It is not known whether the drug is dialyzable.

No specific information is available on the treatment of overdosage with MODURETIC, and no specific antidote is available. Treatment is symptomatic and supportive. Therapy with MODURETIC should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage.

AMILORIDE HCl

No data are available in regard to overdosage in humans.

The oral LD_{50} of amiloride hydrochloride (calculated as the base) is 56 mg/kg in mice and 36 to 85 mg/kg in rats, depending on the strain.

The most common signs and symptoms to be expected with overdosage are dehydration and electrolyte imbalance. If hyperkalemia occurs, active measures should be taken to reduce the serum potassium levels.

HYDROCHLOROTHIAZIDE

The oral LD_{50} of hydrochlorothiazide is greater than 10.0 g/kg in both mice and rats.

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 been administered, hypokalemia may accentuate cardiac arrhythmias.

AVAILABILITY

MODURETIC is available in blister packs of 100's (10's x 10 strips).

Each tablet contains 5 mg amiloride HCl and 50 mg hydrochlorothiazide.