PRODUCT MONOGRAPH

MODURET®

(hydrochlorothiazide and
amiloride hydrochloride tablets, USP)

Each tablet contains 50 mg
of hydrochlorothiazide and
5 mg of amiloride hydrochloride

Diuretic - Antihypertensive

ORBUS PHAMRA, INC.
MARKHAM, ONTARIO, CANADA

Date of Preparation:
January 14, 1981

Date of Revision:
June 16, 2004

Control #: 092195

PRODUCT MONOGRAPH

NAME OF DRUG

MODURET®
(hydrochlorothiazide and
amiloride hydrochloride tablets, USP)

Each tablet contains 50 mg
of hydrochlorothiazide and
5 mg of amiloride hydrochloride

THERAPEUTIC CLASSIFICATION

Diuretic - Antihypertensive

ACTIONS AND CLINICAL PHARMACOLOGY

MODURET® (hydrochlorothiazide and amiloride hydrochloride) is a diuretic/antihypertensive combining the potent natriuretic action of hydrochlorothiazide with the potassium-conserving property of amiloride hydrochloride. The mild diuretic and antihypertensive actions of amiloride hydrochloride 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 MODURET® is within 1 to 2 hours and this action appears to be sustained for approximately 24 hours.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the renal tubular mechanism of electrolyte reabsorption.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium

and bicarbonate. While this compound is predominantly a saluretic agent, in vitro studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs.

Hydrochlorothiazide does not decrease normal blood pressure.

The onset of the diuretic action of hydrochlorothiazide occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Amiloride Hydrochloride

Amiloride hydrochloride is an antikaliuretic drug with mild natriuretic diuretic and antihypertensive activity. These activities may be additive to the effects of thiazides or other saluretic-diuretic agents. The principal use of amiloride hydrochloride is to conserve potassium in selected patients receiving kaliuretic-diuretic agents. The action is not related to the level of aldosterone excretion. Amiloride hydrochloride is not an aldosterone antagonist. The drug acts directly on the distal portion of the nephron. Amiloride hydrochloride causes an increase in sodium excretion and a decrease in potassium and hydrogen ion excretion. Chloride excretion may remain unchanged or increase slowly with continued therapy.

Approximately 50% of an oral dose is absorbed. Amiloride hydrochloride 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.

Pharmacokinetics

Amiloride

Peak plasma levels are obtained in 3 to 4 hours and plasma half-life varies from 6 to 9 hours.

Amiloride hydrochloride is not metabolized by the liver. About 50% of a 20 mg dose of amiloride hydrochloride is excreted unchanged in the urine and 40% is excreted in the stool within 72 hours. In clinical studies amiloride hydrochloride was found to have little effect on glomerular filtration rate or renal blood flow.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life is 5.6-14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND CLINICAL USE

Fixed-dose combination drugs are not indicated for initial therapy. Patients should be titrated on the individual drugs. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. If during maintenance therapy dosage adjustment is necessary it is advisable to use the individual drugs.

MODURET® (hydrochlorothiazide and amiloride hydrochloride) is indicated in the maintenance therapy of:

- patients with hepatic cirrhosis with ascites and edema
- those patients with edema of cardiac origin or with arterial hypertension who are hypokalemic or in whom maintenance of normal potassium levels is considered to be clinically important i.e., digitalized patients, patients in whom adequate dietary intake of potassium is not feasible or patients with cardiac arrhythmias.

Use in Hepatic Cirrhosis with Ascites and Edema

Amiloride hydrochloride used alone may provide satisfactory diuresis with diminished potassium loss and with a reduced risk of metabolic alkalosis. In resistant cases amiloride hydrochloride may be used with kaliuretic-diuretic agents to help produce satisfactory diuresis, while maintaining a more balanced serum electrolyte pattern. As with all therapy for the ascites of hepatic cirrhosis, gradual weight loss and avoidance of electrolyte imbalance are the chief objectives (see PRECAUTIONS).

CONTRAINDICATIONS

Hyperkalemia

MODURET® (hydrochlorothiazide and amiloride hydrochloride) should not be used in the presence of elevated serum potassium levels (see WARNINGS).

Antikaliuretic Therapy or Potassium Salts

Other antikaliuretic agents and potassium supplements are contraindicated in patients receiving MODURET® (such combination therapy is commonly associated with rapid increases in plasma potassium levels).

Impaired Renal Function

Anuria, acute renal failure, severe or progressive renal disease, and diabetic nephropathy are contraindications to the use of MODURET® (see WARNINGS).

Hypersensitivity

MODURET® is contraindicated in patients who are hypersensitive to any component of this medication, or to other sulfonamide-derived drugs.

WARNINGS

Hyperkalemia

Hyperkalemia, i.e., serum potassium levels over 5.5 mEq per litre, has been observed in some patients who received amiloride hydrochloride either alone or with diuretics. This has been noted particularly in elderly patients, in diabetic patients, and in hospitalized patients with hepatic cirrhosis or cardiac edema who had known renal impairment, were seriously ill, or were receiving vigorous diuretic therapy. Since fatalities have occurred in such patients, they should be monitored carefully for clinical, laboratory, and electrocardiographic (ECG) evidence of hyperkalemia and for acidosis. Monitoring of the serum potassium level is important because hyperkalemia is not always associated with an abnormal ECG.

Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities.

When abnormal, the ECG in hyperkalemia is characterized primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the QRS complex, prolongation of the PR interval, and ST depression.

Potassium supplementation in the form of medication or a potassium-rich diet should not be used with MODURET® (hydrochlorothiazide and amiloride hydrochloride) 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

If hyperkalemia occurs in patients taking MODURET® the drug should be discontinued immediately. If the serum potassium level exceeds 6.5 mEq per litre, active measures should be taken to reduce it. Such measures include the intravenous administration of sodium bicarbonate solution or oral or parenteral glucose with a rapid-acting insulin preparation. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given orally or by enema. Patients with persistent hyperkalemia may require dialysis.

Diabetes Mellitus

In diabetic patients, hyperkalemia has been commonly reported with the use of amiloride hydrochloride, particularly if they have chronic renal disease or prerenal azotemia. Some deaths occurred in this last group of patients. Therefore, if therapy with amiloride hydrochloride is considered essential, the drug should be used with caution in diabetic or suspected diabetic patients and only after first determining the status of renal function.

Careful monitoring of serum potassium levels is required throughout the therapy.

One patient with poorly controlled diabetes mellitus who became severely hyperkalemic while on amiloride hydrochloride died following two repeated intravenous glucose tolerance tests. Therefore, amiloride hydrochloride should be discontinued at least 3 days before glucose tolerance testing.

In diabetic patients, insulin requirements may be increased, decreased, or unchanged due to the hydrochlorothiazide component. Diabetes mellitus which has been latent may become manifest during administration of thiazide diuretics.

Metabolic or Respiratory Acidosis

Antikaliuretic therapy should be instituted only with caution in patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or diabetes. If MODURET® is given to the patients, frequent monitoring of acid-base balance is necessary. Shifts in acid-base balance alter the ratio of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

Impaired Renal Function and/or Azotemia

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

In patients with impaired renal function azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. Careful monitoring of such patients is therefore necessary. If increasing azotemia and oliguria occur during treatment MODURET® should be discontinued.

Patients with impaired renal function other than those listed under CONTRAINDICATIONS and who have BUN levels over 30 mg per 100 mL, serum creatinine levels over 1.5 mg per 100 mL, or blood urea values over 60 mg per 100 mL should not receive the drug without careful, frequent monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of MODURET® is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalemia. Prolongation of amiloride hydrochloride excretion was observed in patients with renal impairment.

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.

Hypersensitivity Reactions

Sensitivity reactions to thiazides 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 with the thiazides.

PRECAUTIONS

Electrolyte Imbalance and BUN Increases

Although the likelihood of electrolyte imbalance is lessened with MODURET® (hydrochlorothiazide and amiloride hydrochloride), 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.

Hypochloremia may occur during the use of MODURET®. Any chloride deficit is usually mild and may be corrected by the use of ammonium chloride (except in

patients with hepatic disease) and largely prevented by a near normal salt intake.

Increases in BUN levels have been reported and have usually accompanied vigorous fluid elimination, especially when diuretic combinations were used in seriously ill patients, such as those who have hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant edema. Therefore, careful monitoring of serum electrolytes and BUN levels is important when using MODURET®.

Effects Related to Diuresis in Cirrhotic Patients

Patients with hepatic cirrhosis and ascites are intolerant of acute shifts in electrolyte balance and often have pre-existing hypokalemia as a result of associated secondary hyperaldosteronism. When oral diuretic therapy is used, these patients should be carefully monitored and diuresis should be gradual.

Hepatic encephalopathy, manifested by tremors, confusion, and coma, has been reported in association with amiloride hydrochloride therapy.

In cirrhotic patients receiving amiloride hydrochloride alone, jaundice associated with the underlying disease process has deepened in a few instances, but the relationship to the drug is uncertain.

Metabolism

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

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

Magnesium excretion is increased. 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.

Other

Patients should be observed regularly for the possible occurrence of liver dysfunction, idiosyncratic reactions, or blood dyscrasias.

Use in Obstetrics

Because clinical experience is limited, MODURET® is not recommended for use during 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.

Teratologic studies with amiloride hydrochloride in rabbits and mice revealed no evidence of harm to the fetus. Reproduction studies in rats showed no evidence of impaired fertility. At approximately 5 or more times the expected maximum daily dose for humans, some toxicity was seen in adult rats and rabbits and a decrease in rat pup growth and survival occurred.

In rats a trace of drug crossed the placental barrier.

Thiazides cross the placental barrier and appear in the cord blood. Therefore, the use of MODURET® 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 side effects that have occurred in the adult.

Use in Nursing Mothers

It is not known whether amiloride hydrochloride is excreted in human milk. In rats secretion of amiloride hydrochloride in milk has been demonstrated. Thiazides

appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, if the use of MODURET® is deemed essential, the patient should stop nursing.

Use in Children

The safety for use of amiloride hydrochloride in children has not been established; therefore, MODURET® is not recommended in the pediatric age group.

Drug Interactions

Lithium

Lithium should generally not be given to patients receiving diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended. Refer to the Product Monograph 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 hypertensive 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.

Others

When amiloride hydrochloride 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.

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

Other Antihypertensive Drugs

Hydrochlorothiazide potentiates the action of other antihypertensive drugs. Therefore, the dosage of these agents, especially the ganglion blockers, may need to be reduced when MODURET® is added to the regimen.

Skeletal Muscle Relaxants, Nondepolarizing

Thiazide-containing drugs may increase the responsiveness to tubocurarine.

Pressor Amines

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

Alcohol, Barbiturates, or Narcotics

In the presence of thiazide diuretics, potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (Oral Agents and Insulin)

Dosage adjustment of the antidiabetic drug may be required. Insulin requirements in diabetic patients treated with thiazide diuretics may be increased. Diabetes mellitus which has been latent may become manifest during thiazide administration.

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% respectively.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia may occur when given concomitantly with thiazide diuretics.

Drug/Laboratory Test Interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see PRECAUTIONS).

ADVERSE REACTIONS

While rare, the most serious adverse effect of MODURET® (hydrochlorothiazide and amiloride hydrochloride) is symptomatic hyperkalemia. Other metabolic changes that occur are asymptomatic hyperkalemia, hypokalemia, and hypochloremia.

The following incidence of other adverse reactions was determined from clinical trials (607 patients treated with MODURET®) [see table below].

	Incidence ≥3%	Incidence >1% - <3%	Incidence ≤1%
Gastrointestinal (In 7.1% of patients)	Nausea/anorexia (3.7%)	Diarrhea Gastrointestinal pain Abdominal pain	Constipation GI bleeding GI disturbance Appetite changes Abdominal fullness Hiccups Thirst Vomiting Flatulence Bad taste
Central Nervous System (In 13.9% of patients)	Headache (7.8%) Dizziness (6.1%) Weakness (4.0%)		Paresthesia/ numbness Stupor Vertigo Insomnia Nervousness Depression Sleepiness Mental confusion Visual disturbance
Dermatologic (in 5.2% of patients)	Rash (3.4%)	Pruritus	Flushing
Cardiovascular (In 4.3% of patients)		Arrhythmia	Tachycardia Digitalis toxicity Orthostatic hypotension Angina pectoris
Musculoskeletal (in 3.7% of patients)		Leg ache	Muscle cramps/spasm Joint pain Chest pain Back pain
Respiratory (in 2.6% of patients)		Dyspnea	Nasal congestion
	Incidence ≥3%	**Incidence >1% - <3%**	**Incidence ≤1%**
Urogenital (In 1.7% of patients)			Impotence Nocturia Dysuria Incontinence
Endocrine (in 0.9% of patients)			Gout Dehydration
Other (in 2.6% of patients)		Fatigue/tiredness	Malaise

Other adverse reactions reported with MODURET® are listed below:

Body as a Whole

Syncope

Metabolic

Elevated serum potassium levels (>5.5 mEq per liter)

Electrolyte imbalance

Hyponatremia (See PRECAUTIONS)

Symptomatic hyponatremia

Integumentary

Diaphoresis

Urogenital

Renal dysfunction including renal failure

Other adverse reactions that have been reported with the individual components are listed below:

Amiloride

Body as a Whole

Neck/shoulder ache

Pain in extremities

Digestive

Abnormal liver function

Activation of pre-existing peptic ulcer

Dyspepsia

Jaundice

Integumentary

Dry mouth

Alopecia

Nervous

Tremors

Encephalopathy

Hematologic

Neutropenia

Aplastic anemia

Cardiovascular

One patient with a partial heart block developed complete heartblock

Palpitation

Psychiatric

Decreased libido

Somnolence

Respiratory

Cough

Special Senses

Tinnitus

Increased intraocular pressure

Urogenital

Polyuria

Urinary frequency

Bladder spasm

Hydrochlorothiazide

Body as a Whole

Anaphylactic reactions

Fever

Cardiovascular

Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Digestive

Jaundice (intrahepatic cholestatic jaundice)

Pancreatitis

Cramping

Gastric irritation

Endocrine/Metabolic

Glycosuria

Hyperglycemia

Hyperuricemia

Hypokalemia

Hematologic

Agranulocytosis

Aplastic anemia

Hemolytic anemia

Leukopenia

Purpura

Thrombocytopenia

Integumentary

Photosensitivity

Sialadenitis

Urticaria

Toxic-epidermal necrolysis

Psychiatric

Restlessness

Renal

Interstitial nephritis

Respiratory

Respiratory distress including pneumonitis and pulmonary edema

Special Senses

Transient blurred vision

Xanthopsia

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No data are available in regard to overdosage in humans with MODURET® (hydrochlorothiazide and amiloride hydrochloride) or with the amiloride hydrochloride component.

The most common signs and symptoms to be expected from overdosage with MODURET® are dehydration and electrolyte imbalance. Serum electrolytes should be carefully monitored with special attention to potassium levels. If hyperkalemia occurs, active measures should be taken to reduce the serum potassium levels.

Cardiac arrhythmias may be caused by abnormal potassium levels. Digitalized patients are especially prone to arrhythmias.

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

It is not known whether the drug is dialyzable.

DOSAGE AND ADMINISTRATION

Optimal dosage should be established by the individual titration of the components.

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

Hepatic Cirrhosis with Ascites and Edema

The usual maintenance dose of MODURET® (hydrochlorothiazide and amiloride hydrochloride) is 1 tablet given once a day. The dosage should not exceed 4 tablets a day in single or divided doses.

Edema of Cardiac Origin

The usual maintenance dose of MODURET® is 1 or 2 tablets given once a day or in divided doses. The dosage should not exceed 4 tablets a day. Therapy may be on an intermittent basis.

Hypertension

The usual maintenance dosage is 1 or 2 tablets given once a day or in divided doses. The dosage should not exceed 4 tablets a day.

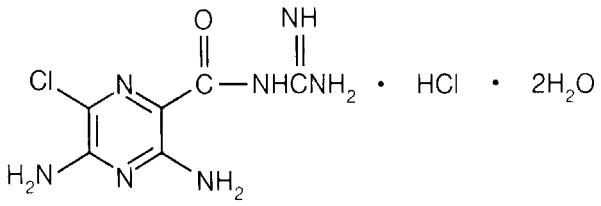
PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Amiloride hydrochloride

Chemical Name: 3,5-diamino-*N*-(aminoiminomethyl)-6 -chloropyrazinecarboxamide monohydrochloride dihydrate.

Structural Formula:



Molecular Formula:
$C_6H_8ClN_7O \bullet HCl \bullet 2H_2O$

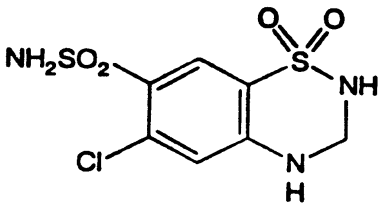
Molecular Weight: 302.12

Description: Amiloride hydrochloride is a yellow to greenish yellow, odourless or practically odorless, crystalline compound, soluble in water. It is the salt of a moderately strong base, amiloride, pKa 8.7.

Hydrochlorothiazide

Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Structural formula:



Molecular formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.74

Description: Hydrochlorothiazide is a white or practically white crystalline compound with low solubility in water, but is readily soluble in dilute aqueous sodium hydroxide.

II. COMPOSITION

Each tablet contains 50 mg hydrochlorothiazide, 5 mg amiloride hydrochloride, and the following non-medicinal ingredients: lactose, dibasic calcium phosphate, guar gum, starch, magnesium stearate and sunset yellow FCF.

III. STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C and 30°C in a tightly closed container.

AVAILABILITY OF DOSAGE FORM

MODURET® (hydrochlorohtiazide and amiloride hydrochloride) tablets are peach-coloured, diamond-shaped, compressed tablets, scored on one side with MSD 917 and M on the other, containing 50 mg hydrochlorothiazide and 5 mg amiloride hydrochloride. Available in bottles of 100.

PHARMACOLOGY

Hydrochlorothiazide

Hydrochlorothiazide has diuretic and antihypertensive activities. This compound increases the excretion of sodium and chloride in approximately equivalent amounts and causes a simultaneous, usually minimal loss of bicarbonate. The excretion of

ammonia is reduced slightly by hydrochlorothiazide and the blood ammonia concentration may be increased. The excretion of potassium is increased slightly. Calcium excretion is decreased by hydrochlorothiazide and magnesium excretion is increased.

Hydrochlorothiazide is eliminated rapidly by the kidney. Its rate of elimination is decreased somewhat by the coadministration of probenecid without, however, an accompanying reduction in diuresis.

Amiloride Hydrochloride

Amiloride hydrochloride is chemically unrelated to other known antikaliuretic or diuretic agents. It is a salt of a moderately strong base (pKa 8.7).

In rats and dogs, amiloride hydrochloride in an oral dose of 0.1 mg/kg or less increases the excretion of sodium and, to a lesser extent, of chloride but does not increase the excretion of potassium.

A potassium-retaining effect is seen in experimental animals, especially under conditions of high potassium excretion, as upon loading with potassium chloride, after pretreatment with acetazolamide or thiazides, or in deoxycorticosterone-treated adrenalectomized rats. The natriuresis is accompanied by an increase in urinary pH, reflecting a decrease in hydrogen ion excretion.

Following oral administration to dogs, amiloride hydrochloride increases the rate of sodium excretion less than do the more potent agents, but the moderate effect on sodium excretion has an extended duration. Natriuresis increases only moderately as the oral dose is increased from 0.25 to 4.0 mg/kg, this activity persists beyond 6 hours.

An increase in sodium excretion is produced when amiloride hydrochloride is given together with chlorothiazide, hydrochlorothiazide, or acetazolamide to rats. Amiloride hydrochloride antagonizes the kaliuretic effect of the other diuretic. Oral doses of amiloride hydrochloride (0.1 to 0.5 mg/kg) increase the excretion of sodium

and decrease that of potassium in dogs given ethacrynic acid (1.0 mg/kg) or hydrochlorothiazide (0.5 mg/kg) orally.

Amiloride hydrochloride increases the Na^+/K^+ excretion ratio in adrenalectomized rats. In adrenalectomized rats treated with aldosterone, deoxycorticosterone, or hydrocortisone, amiloride hydrochloride not only reverses the steroid-induced sodium retention, but increases the Na^+/K^+ excretion ratio substantially above that of untreated adrenalectomized rats.

Stop-flow studies in dogs indicate that amiloride hydrochloride inhibits tubular secretion of potassium and reabsorption of sodium in the distal portion of the nephron. In renal clearance studies, 1.0 mg/kg intravenously did not affect glomerular filtration rate, effective renal plasma flow, or glucose reabsorption. An enzymatic basis for the renal action of amiloride hydrochloride has not been elucidated. It is not an inhibitor of carbonic anhydrase.

Amiloride hydrochloride given parenterally (2.5 to 5.0 mg/kg) to anesthetized dogs produces profound reduction of blood pressure and produces changes in the electrocardiogram. The effects which are coincident with the release of histamine into plasma, are not seen if the compound is injected slowly or if lower doses are given. A slight increase in gastric secretion and intestinal motility occurred after oral administration to dogs of 0.5 to 2.0 mg/kg. Pretreatment of several days with amiloride hydrochloride in a dose of 5 mg/kg/day by mouth does not alter the response of dogs to ouabain.

TOXICOLOGY

Acute Toxicity

ORAL LD_{50} (mg/kg)			
SPECIES	**Amiloride Hydrochloride**	**Hydrochlorothiazide**	**Amiloride Hydrochloride/ Hydrochlorothiazide 5:50**
MICE	56	>10,000	189
RATS	36 - 85	>10,000	422 (females) 377 (males)

Acute oral studies of fixed combinations in the mouse and rat showed that the toxicity was based primarily on the amiloride content.

Subacute and Chronic Toxicity

Amiloride Hydrochloride/Hydrochlorothiazide

Twelve-week and 25-week oral studies of the combination in the rat indicated the toxicity expected from the individual ingredients (fluid loss at high doses and hyperplasia of the adrenal zona glomerulosa). No evidence of drug interaction was seen. The high dose in the 12-week study (10 mg/kg of amiloride hydrochloride with 500 mg/kg of hydrochlorothiazide) was not well tolerated; 7 of 15 males and 4 of 15 females died.

The toxicity was related to effects on serum electrolytes.

In the dog, effects observed included dry nose and gums, diuresis, natriuresis, chloruresis, antikaluresis, and hyperplasia of the adrenal zona glomerulosa. Electrocardiographic changes suggestive of potassium retention were seen at high dose levels. A dose of 5/50 mg/kg resulted in deaths from electrolyte imbalance. A dose of 2.5/25 mg/kg increased to 4/40 mg/kg/day was tolerated for six months.

Amiloride Hydrochloride

MODERATE TO MARKED HYPERKALEMIA DEVELOPED AT DOSES GREATER THAN 8.0 mg/kg/day. ELECTROCARDIOGRAPHIC CHANGES WERE OBSERVED. SERUM SODIUM AND CHLORIDE DECREASED.

Rats were administered 0, 2.5, 5, 10 or 20 mg/kg/day of amiloride for 5 weeks by the oral route. The lower doses showed mild toxicity; gastric lesions, similar to stress ulcers, were observed at 10 and 20 mg/kg/day.

Superficial ulceration of the stomach or intestine was seen in 2 of 12 dogs in a 6 week oral study.

Rats received amiloride hydrochloride by oral route at doses of 0, 2.5, 5.0 and 10 to 15 mg/kg for up to 80 weeks. Inhibition of weight gain occurred in male rats. Treatment related changes included alterations in urinary and serum sodium and potassium, renal tubular dilatation and a dose-dependent hyperplasia of the adrenal zona glomerulosa. Hypotonia of muscles, loss of righting reflex and coma occurred in moribund rats (high dose group). Symptoms of electrolyte imbalance including paraphimosis, occurred at doses of 10 mg/kg/day during a one year study.

Dogs treated with oral doses of 0, 2, 4 and 8 mg/kg/day (base) for one year showed changes in body weight, water intake and serum electrolytes. Positive fecal occult blood occurred at a slightly greater incidence in treated animals but no evidence of gastrointestinal ulceration was seen. Doses producing marked electrolyte changes had no effect on blood glucose or glucose tolerance. Dose-dependent hyperplasia of the zona glomerulosa of the adrenal was observed in all treated dogs.

In monkeys treated with oral doses of 0, 2, 4 and 8 (increased to 15.8) mg/kg/day for one year, excitable and irritable behavior occurred at the highest dose. Increase in serum potassium and decrease in serum sodium occurred at doses as low as 4 mg/kg/day. Although adrenal glands of some high and middle dose animals appeared enlarged, hyperplasia of the zona glomerulosa was not observed. Urinary excretion of aldosterone was increased in high dose animals.

Special Studies Relative to Adrenal Zona Glomerulosa, Hyperplasia and Diabetes

Amiloride hydrochloride produced a dose-dependent hyperplasia of the zona glomerulosa of the adrenal cortex in rats and dogs and to a lesser extent in monkeys. In rats, reversibility of the hyperplasia was demonstrated after the drug was given for 58 weeks and the animals were observed for an additional 22 weeks. Hyperplasia has been shown to disappear in 19 to 30 days after cessation of treatment and the adrenals were normal within 30 to 58 days. The hyperplasia can be reduced by substitution of physiologic saline for drinking water. Hyperplasia of the adrenal zona glomerulosa occurred in maternal mice but not in the offspring in a teratogenic study. The hyperplasia is considered to be induced by alteration of serum electrolytes and/or inhibition of aldosterone activity.

No effect on carbohydrate metabolism was observed when the toxicity of amiloride hydrochloride was studied in obese diabetic Zucker rats and normal-thin rats. Amiloride hydrochloride had no adverse effect on glucose tolerance in acute experiments in rats or in a chronic study in dogs.

The effect of amiloride hydrochloride on I^{131} uptake was measured in immature female rats. A dose of about 5 or 10 mg/kg/day given subcutaneously every 8 hours for 21 days did not alter I^{131} uptake.

Hydrochlorothiazide

In dogs given doses of 250, 500 and 1000 mg/kg seven days a week for 8 weeks, no gross signs of drug effect were noted except for electrolyte imbalance.

Chronic oral toxicity studies in the rat using doses of up to 2000 mg/kg/day 5 days per week for 26 weeks showed no signs of drug effect and no drug-related changes on post mortem examination. In dogs, oral doses of 0, 125, 250 mg/kg/day 5 days per week for 26 weeks; 500 mg/kg/day for 7 weeks; 11 weeks without drug then 500 mg/kg/day for 7 days per week for 8 weeks were given. Slight depression of plasma potassium, small amounts of yellow crystalline precipitate in the bladder in two of twelve dogs were found on gross examination. Histomorphologic studies did not show drug-related changes.

Tumorigenicity Studies

No tumorigenic effect was observed when amiloride hydrochloride was administered for 92 weeks to mice at doses of up to 10 mg/kg/day and for 104 weeks to rats at doses of up to 8 mg/kg/day.

Reproductive Studies

Amiloride hydrochloride/hydrochlorothiazide combinations were administered orally to pregnant mice at dosage levels of 1/5, 5/25, and 5/50 mg/kg/day (12.5 times the expected maximum daily dose for humans) and to pregnant rabbits at dosage levels of 1.0/2.5, 1/5, and 4/20 mg/kg/day (10/20 times the expected maximum daily dose for humans). In a second study in pregnant rabbits, amiloride hydrochloride/hydrochlorothiazide was administered at dosage levels of 0.5/5, 1/10, and 2/20 mg/kg/day (5 times the expected maximum daily dose for humans). No teratogenic, embryotoxic, fetotoxic, or maternotoxic effects attributable to treatment were observed in either species.

No effect on reproductive performance or fertility in albino rats (COBS strain) given 2, 4, or 8 mg/kg/day amiloride base orally was noted. Growth rate and food consumption were reduced at the highest dose. Doses of 4 and 8 mg/kg/day were administered without effect during late gestation and growth. The high dose adversely affected pup survival and growth.

SELECTED BIBLIOGRAPHY

1. Antcliff AC, Beevers DG, Hamilton M, Harpur JE. The use of amiloride hydrochloride in the correction of hypokalaemic alkalosis induced by diuretics. Postgrad Med J 1971;47:644-7.

2. Bergstrom J, Fridén AM. The effect of hydrochlorothiazide and amiloride administered together on muscle electrolytes in normal subjects. Acta Med Scand 1975;197:415-9.

3. Borhani NO. Chlorothiazide and hydrochlorothiazide: A comparative study of their hypotensive saluretic and hyperuricemic action. Ann Int Med 1960;53(2):342-58.

4. Bull MB, Laragh JH. Amiloride, a potassium-sparing natriuretic agent. Circulation 1968;37:45-53.

5. Bryant JM, et al. The hypotensive effects of chlorothiazide and hydrochlorothiazide: A critical comparison. Am J Cardiol 1961;7(3):392-5.

6. Castenfors H. Long-term treatment with a fixed combination of amiloride hydrochloride and hydrochlorothiazide, Recent studies: Diuresis, kaliuresis, and hypertension: Long-term clinical experience with a fixed combination of amiloride hydrochloride and hydrochlorothiazide. Proceedings of an international workshop held in Bologna, Italy, Dec 14, 1976; Bruno Magnani (ed.), Futura Publishing Co., Inc., Mt Kisco, N.Y. 1977;27-35.

7. Eisalo A, Kohvakka A. Serum potassium levels with a fixed combination of amiloride hydrochloride and hydrochlorothiazide, Recent studies: Diuresis, kaliuresis, and hypertension: Long-term clinical experience with a fixed combination of amiloride hydrochloride and hydrochlorothiazide. Proceedings of an international workshop held in Bologna, Italy, Dec 14, 1976; Bruno Magnani (ed), Futura Publishing Co., Inc., Mt Kisco, N.Y. 1977;1-11.

8. Gombos EA, Freis ED, Moghadam A. Effect of MK-870 in normal subjects and hypertensive patients. N Engl J Med 1966;275:1215-20.

9. Grenfell RF, Briggs AH, Holland WC. Hypotensive effects of some antihypertensive drugs. Clin Pharmacol Ther 1963;4(2):162-71.

10. Hamdy RC, Tovey J, Perera N. Hypokalaemia and diuretics. Br Med J 1980;280:1187.

11. Lammintausta R, Kanto J, Mäntylä R. Renin-aldosterone system and urinary electrolytes after amiloride, hydrochlorothiazide and the combination. Int J Clin Pharmacol Biopharm 1978;16(11):503-7.

12. MacFarlane JPR. Long-term use of a fixed combination of amiloride hydrochloride and hydrochlorothiazide in elderly patients, Recent studies: Diuresis, kaliuresis, and hypertension: Long-term clinical experience with a fixed combination of amiloride hydrochloride and hydrochlorothiazide. Proceedings of an international workshop held in Bologna, Italy, Dec 14, 1976; Bruno Magnani (ed), Futura Publishing Co., Inc., Mt Kisco, N.Y. 1977;82-9.

13. Paterson JW, Dollery CT, Haslam RM. Amiloride hydrochloride in hypertensive patients. Br Med J 1968;1:422-3.

14. Pearce VR, Antcliff AC, Beevers DG, Hamilton M. Total exchangeable potassium in response to amiloride. Postgrad Med J 1978;54(634):533-7.

15. Sherlock S. Diseases of the liver and biliary system (5th Edition), Blackwell Scientific Publications, 1975.

16. Smirk H, McQueen EG, Morrison RBI. Chlorothiazide and hydrochlorothiazide in management of hypertension. Br Med J 1960;1:515-8.

17. Van Soeren F. The antihypertensive and biochemical effects of hydrochlorothiazide/amiloride (MODURETIC®) versus chlorthalidone. J Int Med Res 1980;8:132-5.

18. Waal-Manning HJ, Simpson FO. A fixed combination of amiloride hydrochloride and hydrochlorothiazide in the treatment of hypertension, Recent studies: Diuresis, kaliuresis, and hypertension: Long-term clinical experience with a fixed combination of amiloride hydrochloride and hydrochlorothiazide. Proceedings of an international workshop held in Bologna, Italy, Dec 14, 1976; Bruno Magnani (ed), Futura Publishing Co., Inc., Mt Kisco, N.Y. 1977;48-63.

19. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. Postgrad Med J 1980;56:348-50.

20. Whight C, Morgan T, Carney S, Wilson M. Diuretics, cardiac failure and potassium depletion: A rational approach. Med J Aust 1974;2:831-3.

21. Wolf RL, Mendlowitz M, Roboz J, Gitlow SE. Treatment of hypertension with antihypertensive diuretic drugs. Am Heart J 1966;72:692-7.

22. Yamada S, Reynolds TB. Amiloride (MK-870), A new antikaluretic diuretic: Comparison to other antikaluretic diuretics in patients with liver disease and ascites. Gastroenterology 1970;59:833-41.

23. Zsotér TT, Hart F, Raddle IC. Mechanism of antihypertensive action of prolonged administration of hydrochlorothiazide in rabbit and dog. Circulation Research, 1970;XXVII:717-25.