CENTER FOR DRUG EVALUATION AND RESEARCH

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7905118

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

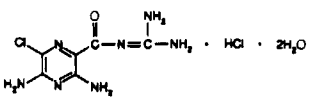
TABLETS

MIDAMOR®

(AMILORIDE HCl)

DESCRIPTION

Amiloride HCl, an antikaliuretic-diuretic agent, is a pyrazine-carbonyl-guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. It is the salt of a moderately strong base (pKa 8.7). It is designated chemically as 3,5-diamino-6-chloro-*N*-(diaminomethylene) pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 302.12. Its empirical formula is $C_6H_8ClN_7O{\cdot}HCl{\cdot}2H_2O$ and its structural formula is:



MIDAMOR® (Amiloride HCl) is available for oral use as tablets containing 5 mg of anhydrous amiloride HCl. Each tablet contains the following inactive ingredients: calcium phosphate, D&C Yellow 10, iron oxide, lactose, magnesium stearate and starch.

CLINICAL PHARMACOLOGY

MIDAMOR is a potassium-conserving (antikaliuretic) drug that possesses weak (compared with thiazide diuretics) natriuretic, diuretic, and antihypertensive activity. These effects have been partially additive to the effects of thiazide diuretics in some clinical studies. When administered with a thiazide or loop diuretic, MIDAMOR has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone. MIDAMOR has potassium-conserving activity in patients receiving kaliuresic-diuretic agents.

MIDAMOR is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

MIDAMOR exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism accounts in large part for the potassium sparing action of amiloride.

MIDAMOR 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. Effects on electrolytes increase with single doses of amiloride HCl up to approximately 15 mg.

Amiloride HCl is not metabolized by the liver but is excreted unchanged by the kidneys. About 50 percent of a 20 mg dose of MIDAMOR is excreted in the urine and 40 percent in the stool within 72 hours. MIDAMOR has little effect on glomerular filtration rate or renal blood flow. Because amiloride HCl is not metabolized by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

INDICATIONS AND USAGE

MIDAMOR is indicated as adjunctive treatment with thiazide diuretics or other kaliuretic-diuretic agents in congestive heart failure or hypertension to:

a. help restore normal serum potassium levels in patients who develop hypokalemia on the kaliuretic diuretic
b. prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium-conserving agents is often unnecessary in patients receiving diuretics for uncomplicated essential hypertension when such patients have a normal diet. MIDAMOR has little additive diuretic or antihypertensive effect when added to a thiazide diuretic.

MIDAMOR should rarely be used alone. It has weak (compared with thiazides) diuretic and antihypertensive effects. Used as single agents, potassium sparing diuretics, including MIDAMOR, result in an increased risk of hyperkalemia (approximately 10% with amiloride). MIDAMOR should be used alone only when persistent hypokalemia has been documented and only with careful titration of the dose and close monitoring of serum electrolytes.

CONTRAINDICATIONS

Hyperkalemia

MIDAMOR should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq per liter).

Antikaliuretic Therapy or Potassium Supplementation

MIDAMOR should not be given to patients receiving other potassium-conserving agents, such as spironolactone or triamterene. Potassium supplementation in the form of medication, potassium-containing salt substitutes or a potassium-rich diet should not be used with MIDAMOR except in severe and/or refractory cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function

Anuria, acute or chronic renal insufficiency, and evidence of diabetic nephropathy are contraindications to the use of MIDAMOR. Patients with evidence of renal functional impairment (blood urea nitrogen [BUN] levels over 30 mg per 100 mL or serum creatinine levels over 1.5 mg per 100 mL) or diabetes mellitus should not receive the drug without careful, frequent and continuing monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of an antikaliuretic agent is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalemia.

Hypersensitivity

MIDAMOR is contraindicated in patients who are hypersensitive to this product.

WARNINGS

Hyperkalemia

Like other potassium-conserving agents, amiloride may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. When MIDAMOR is used concomitantly with a thiazide diuretic in patients without these complications, the risk of hyperkalemia is reduced to about 1-2 percent. It is thus essential to monitor serum potassium levels carefully in any patient receiving amiloride, particularly when it is first introduced, at the time of diuretic dosage adjustments, and during any illness that could affect renal function.

The risk of hyperkalemia may be increased when potassium-conserving agents, including MIDAMOR, are administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus. (See PRECAUTIONS, *Drug Interactions*.) Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities. Monitoring of the serum potassium level is essential because mild hyperkalemia is not usually associated with an abnormal ECG.

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.

Treatment of hyperkalemia: If hyperkalemia occurs in patients taking MIDAMOR, the drug should be discontinued immediately. If the serum potassium level exceeds 6.5 mEq per liter, 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 reported with the use of all potassium-conserving diuretics, including MIDAMOR, even in patients without evidence of diabetic nephropathy. Therefore, MIDAMOR should be avoided, if possible, in diabetic patients and, if it is used, serum electrolytes and renal function must be monitored frequently.

MIDAMOR should be discontinued at least three days before glucose tolerance testing.

Metabolic or Respiratory Acidosis

Antikaliuretic therapy should be instituted only with caution in severely ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or poorly controlled diabetes. If MIDAMOR is given to these 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.

PRECAUTIONS

General

Electrolyte Imbalance and BUN Increases

Hyponatremia and hypochloremia may occur when MIDAMOR is used with other diuretics and increases in BUN levels have been reported. These increases usually have accompanied vigorous fluid elimination, especially when diuretic therapy was used in seriously ill patients, such as those who had hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant edema. Therefore, when MIDAMOR is given with other diuretics to such patients, careful monitoring of serum electrolytes and BUN levels is important. In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice, have been reported in association with diuretics, including amiloride HCl.

Drug Interactions

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. (See WARNINGS.)

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

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 MIDAMOR 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. Since indomethacin and potassium-sparing diuretics, including MIDAMOR, may each be associated with increased serum potassium levels, the potential effects on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Carcinogenicity, Mutagenicity, Impairment of Fertility

There was no evidence of a tumorigenic effect when amiloride HCl was administered for 92 weeks to mice at doses up to 10 mg/kg/day (25 times the maximum daily human dose). Amiloride HCl has also been administered for 104 weeks to male and female rats at doses up to 6 and 8 mg/kg/day (15 and 20 times the maximum daily dose for humans, respectively) and showed no evidence of carcinogenicity.

Amiloride HCl was devoid of mutagenic activity in various strains of *Salmonella typhimurium* with or without a mammalian liver microsomal activation system (Ames test).

Pregnancy

Pregnancy Category B. Teratogenicity studies with amiloride HCl in rabbits and mice given 20 and 25 times the maximum human dose, respectively, revealed no evidence of harm to the fetus, although studies showed that the drug crossed the placenta in mice and concentrated. Reproduction studies in rats at 20 times the expected maximum daily dose for humans 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.

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.

Nursing Mothers

Studies in rats have shown that amiloride is excreted in milk in concentrations higher than those found in blood, but it is not known whether MIDAMOR is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MIDAMOR, a decision should be made whether to discontinue nursing or to discontinue the drug, 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

Clinical studies of MIDAMOR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, *Impaired Renal Function*.)

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ADVERSE REACTIONS

MIDAMOR is usually well tolerated and, except for hyperkalemia (serum potassium levels greater than 5.5 mEq per liter — see WARNINGS), significant adverse effects have been reported infrequently. Minor adverse reactions were reported relatively frequently (about 20%) but the relationship of many of the reports to amiloride HCl is uncertain and the overall frequency was similar in hydrochlorothiazide treated groups. Nausea/anorexia, abdominal pain, flatulence, and mild skin rash have been reported and probably are related to amiloride. Other adverse experiences that have been reported with amiloride are generally those known to be associated with diuresis, or with the underlying disease being treated.

The adverse reactions for MIDAMOR listed in the following table have been arranged into two groups: (1) incidence greater than one percent, and (2) incidence one percent or less. The incidence for group (1) was determined from clinical studies conducted in the United States (837 patients treated with MIDAMOR). The adverse effects listed in group (2) include reports from the same clinical studies and voluntary reports since marketing. The probability of a causal relationship exists between MIDAMOR and these adverse reactions, some of which have been reported only rarely.

Incidence >1%	*Incidence ≤1%*
Body as a Whole	
Headache**	Back pain
Weakness	Chest pain
Fatigability	Neck/shoulder ache
	Pain, extremities
Cardiovascular	
None	Angina pectoris
	Orthostatic hypotension
	Arrhythmia
	Palpitation
Digestive	
Nausea/anorexia**	Jaundice
Diarrhea**	GI bleeding
Vomiting**	Abdominal fullness
Abdominal pain	GI disturbance
Gas pain	Thirst
Appetite changes	Heartburn
Constipation	Flatulence
	Dyspepsia
Metabolic	
Elevated serum potassium levels (>5.5 mEq per liter)***	None
Skin	
None	Skin rash
	Itching
	Dryness of mouth
	Pruritus
	Alopecia
Musculoskeletal	
Muscle cramps	Joint pain
	Leg ache
Nervous	
Dizziness	Paresthesia
Encephalopathy	Tremors
	Vertigo
Psychiatric	
None	Nervousness
	Mental confusion
	Insomnia
	Decreased libido
	Depression
	Somnolence
Respiratory	
Cough	Shortness of breath
Dyspnea	
Special Senses	
None	Visual disturbances
	Nasal congestion
	Tinnitus
	Increased intraocular pressure
Urogenital	
Impotence	Polyuria
	Dysuria
	Urinary frequency
	Bladder spasms
	Gynecomastia

**Reactions occurring in 3% to 8% of patients treated with MIDAMOR (Those reactions occurring in less than 3% of the patients are unmarked.)
***See WARNINGS

Causal Relationship Unknown

Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Activation of probable pre-existing peptic ulcer
Aplastic anemia
Neutropenia
Abnormal liver function

OVERDOSAGE

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 38 to 85 mg/kg in rats, depending on the strain.

It is not known whether the drug is dialyzable.

The most likely signs and symptoms to be expected with overdosage are dehydration and electrolyte imbalance. These can be treated by established procedures. Therapy with MIDAMOR should be discontinued and the patient observed closely. There is no specific amiloride. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive. If hyperkalemia occurs, active measures should be taken to reduce the serum potassium levels.

DOSAGE AND ADMINISTRATION

MIDAMOR should be administered with food.

MIDAMOR, one 5 mg tablet daily, should be added to the usual antihypertensive or diuretic dosage of a kaliuretic diuretic. The dosage may be increased to 10 mg per day, if necessary. More than two 5 mg tablets of MIDAMOR daily usually are not needed, and there is little controlled experience with such doses. If persistent hypokalemia is documented with 10 mg, the dose can be increased to 15 mg, then 20 mg, with careful monitoring of electrolytes.

In treating patients with congestive heart failure after an initial diuresis has been achieved, potassium loss may also decrease and the need for MIDAMOR should be re-evaluated. Dosage adjustment may be necessary. Maintenance therapy may be on an intermittent basis.

If it is necessary to use MIDAMOR alone (see INDICATIONS), the starting dosage should be one 5 mg tablet daily. This dosage may be increased to 10 mg per day, if necessary. More than two 5 mg tablets usually are not needed, and there is little controlled experience with such doses. If persistent hypokalemia is documented with 10 mg, the dose can be increased to 15 mg, then 20 mg, with careful monitoring of electrolytes.

HOW SUPPLIED

No. 3381 — Tablets MIDAMOR, 5 mg, are yellow, diamond-shaped, compressed tablets, coded MSD 92 on one side and MIDAMOR on the other. They are supplied as follows:

NDC 0006-0092-68 bottles of 100

Storage

Protect from moisture, freezing and excessive heat.

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued August 2001
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TABLETS

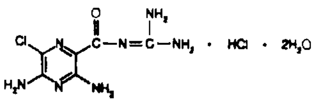
MODURETIC®

(AMILORIDE HCl-HYDROCHLOROTHIAZIDE)

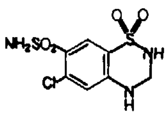
DESCRIPTION

MODURETIC* (Amiloride HCl-Hydrochlorothiazide) combines the potassium-conserving action of amiloride HCl with the natriuretic action of hydrochlorothiazide.

Amiloride HCl is designated chemically as 3,5-diamino-6-chloro-*N*-(diaminomethylene)pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 302.12. Its empirical formula is $C_6H_8ClN_7O{\cdot}HCl{\cdot}2H_2O$ and its structural formula is:



Hydrochlorothiazide is designated chemically as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

MODURETIC is available for oral use as tablets containing 5 mg of anhydrous amiloride HCl and 50 mg of hydrochlorothiazide. Each tablet contains the following inactive ingredients: calcium phosphate, FD&C Yellow 6, guar gum, lactose, magnesium stearate and starch.

CLINICAL PHARMACOLOGY

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 (see PRECAUTIONS). The onset of the diuretic action of MODURETIC is within 1 to 2 hours and this action appears to be sustained for approximately 24 hours.

Amiloride HCl

Amiloride HCl is a potassium-conserving (antikaliuretic) drug that possesses weak (compared with thiazide diuretics) natriuretic, diuretic, and antihypertensive activity. These effects have been partially additive to the effects of thiazide diuretics in some clinical studies. Amiloride HCl has potassium-conserving activity in patients receiving kaliuretic-diuretic agents.

Amiloride HCl is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

Amiloride HCl exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism accounts in large part for the potassium sparing action of amiloride.

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. Effects on electrolytes increase with single doses of amiloride HCl up to approximately 15 mg.

Amiloride HCl is not metabolized by the liver but is excreted unchanged by the kidneys. About 50 percent of a 20 mg dose of amiloride HCl is excreted in the urine and 40 percent in the

stool within 72 hours. Amiloride HCl has little effect on glomerular filtration rate or renal blood flow. Because amiloride HCl is not metabolized by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal 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.

After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent 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 USAGE

MODURETIC is indicated in those patients with hypertension or with congestive heart failure who develop hypokalemia when thiazides or other kaliuretic diuretics are used alone, or in whom maintenance of normal serum potassium levels is considered to be clinically important, e.g., digitalized patients, or patients with significant cardiac arrhythmias.

The use of potassium-conserving agents is often unnecessary in patients receiving diuretics for uncomplicated essential hypertension when such patients have a normal diet.

MODURETIC may be used alone or as an adjunct to other antihypertensive drugs, such as methyldopa or beta blockers. Since MODURETIC enhances the action of these agents, dosage adjustments may be necessary to avoid an excessive fall in blood pressure and other unwanted side effects.

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

CONTRAINDICATIONS

Hyperkalemia

MODURETIC should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq per liter).

Antikaliuretic Therapy or Potassium Supplementation

MODURETIC should not be given to patients receiving other potassium-conserving agents, such as spironolactone or triamterene. Potassium supplementation in the form of medication, potassium-containing salt substitutes or a potassium-rich diet should not be used with MODURETIC except in severe and/or refractory cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function

Anuria, acute or chronic renal insufficiency, and evidence of diabetic nephropathy are contraindications to the use of MODURETIC. Patients with evidence of renal functional impairment (blood urea nitrogen [BUN] levels over 30 mg per 100 mL or serum creatinine levels over 1.5 mg per 100 mL) or diabetes mellitus should not receive the drug without careful, frequent and continuing monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of an antikaliuretic agent is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalemia.

Hypersensitivity

MODURETIC is contraindicated in patients who are hypersensitive to this product, or to other sulfonamide-derived drugs.

WARNINGS

Hyperkalemia

> Like other potassium-conserving diuretic combinations, MODURETIC may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter). In patients without renal impairment or diabetes mellitus, the risk of hyperkalemia with MODURETIC is about 1-2 percent. This risk is higher in patients with renal impairment or diabetes mellitus (even without recognized diabetic nephropathy). Since hyperkalemia, if uncorrected, is potentially fatal, it is essential to monitor serum potassium levels carefully in any patient receiving MODURETIC, particularly when it is first introduced, at the time of dosage adjustments, and during any illness that could affect renal function.

The risk of hyperkalemia may be increased when potassium-conserving agents, including MODURETIC, are administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus. (See PRECAUTIONS, *Drug Interactions*.) Warning signs or

symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities. Monitoring of the serum potassium level is essential because mild hyperkalemia is not usually associated with an abnormal ECG.

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.

Treatment of hyperkalemia: If hyperkalemia occurs in patients taking MODURETIC, the drug should be discontinued immediately. If the serum potassium level exceeds 6.5 mEq per liter, 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 reported with the use of all potassium-conserving diuretics, including amiloride HCl, even in patients without evidence of diabetic nephropathy. Therefore, MODURETIC should be avoided, if possible, in diabetic patients and, if it is used, serum electrolytes and renal function must be monitored frequently.

MODURETIC should be discontinued at least three days before glucose tolerance testing.

Metabolic or Respiratory Acidosis

Antikaliuretic therapy should be instituted only with caution in severely ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or poorly controlled diabetes. If MODURETIC is given to these 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.

PRECAUTIONS

General

Electrolyte Imbalance and BUN Increases

Determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance: i.e., hyponatremia, 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.

Hyponatremia and hypochloremia may occur during the use of thiazides and other diuretics. Any chloride deficit during thiazide therapy is generally mild and may be lessened by the amiloride HCl component of MODURETIC. Hypochloremia 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.

Hypokalemia may develop during thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy. However, this usually is prevented by the amiloride HCl component of MODURETIC.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Amiloride HCl, a component of MODURETIC, has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone.

Increases in BUN levels have been reported with amiloride HCl and with hydrochlorothiazide. These increases usually have accompanied vigorous fluid elimination, especially when diuretic therapy was used in seriously ill patients, such as those who had hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant edema. Therefore, when MODURETIC is given to such patients, careful monitoring of serum electrolyte and BUN levels is important. In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice, have been reported in association with diuretic therapy including amiloride HCl and hydrochlorothiazide.

In patients with renal disease, diuretics may precipitate azotemia. Cumulative effects of the components of MODURETIC may develop in patients with impaired renal

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(AMILORIDE HCl-HYDROCHLOROTHIAZIDE)
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function. If renal impairment becomes evident, MODURETIC should be discontinued (see CONTRAINDICATIONS and WARNINGS).

Drug Interactions

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 MODURETIC 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. Since indomethacin and potassium-sparing diuretics, including MODURETIC, may each be associated with increased serum potassium levels, the potential effects on potassium kinetics and renal function should be considered when these agents are administered concurrently.

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. (See WARNINGS.)

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 or potentiation.

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.

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 MODURETIC.

Metabolic and Endocrine Effects

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

Because calcium excretion is decreased by thiazides, MODURETIC should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

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

Other Precautions

In patients receiving thiazides, sensitivity reactions may occur 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 use of thiazides.

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

Carcinogenicity, Mutagenicity, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the effects upon fertility, mutagenicity or carcinogenic potential of MODURETIC.

Amiloride HCl

There was no evidence of a tumorigenic effect when amiloride HCl was administered for 92 weeks to mice at doses up to 10 mg/kg/day (25 times the maximum daily human dose). Amiloride HCl has also been administered for 104 weeks to male and female rats at doses up to 6 and 8 mg/kg/day (15 and 20 times the maximum daily dose for humans, respectively) and showed no evidence of carcinogenicity.

Amiloride HCl was devoid of mutagenic activity in various strains of *Salmonella typhimurium* with or without a mammalian liver microsomal activation system (Ames test).

Hydrochlorothiazide

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* 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 1300 μg/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

Pregnancy Category B. Teratogenicity studies have been performed with combinations of amiloride HCl and hydrochlorothiazide in rabbits and mice at doses up to 25 times the expected maximum daily dose for humans and have revealed no evidence of harm to the fetus. No evidence of impaired fertility in rats was apparent at dosage levels up to 25 times the expected maximum human daily dose. A perinatal and postnatal study in rats showed a reduction in maternal body weight gain during and after gestation at a daily dose of 25 times the expected maximum daily dose for humans. The body weights of alive pups at birth and at weaning were also reduced at this dose level. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, and because of the data listed below with the individual components, this drug should be used during pregnancy only if clearly needed.

Amiloride HCl

Teratogenicity studies with amiloride HCl in rabbits and mice given 20 and 25 times the maximum human dose, respectively, revealed no evidence of harm to the fetus, although studies showed that the drug crossed the placenta in modest amounts. Reproduction studies in rats at 20 times the expected maximum daily dose for humans 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.

Hydrochlorothiazide

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 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.

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

Studies in rats have shown that amiloride is excreted in milk in concentrations higher than those found in blood, but it is not known whether amiloride HCl is excreted in human milk. However, thiazides appear 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 the drug, 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

Clinical studies of MODURETIC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, *Impaired Renal Function*.)

ADVERSE REACTIONS

MODURETIC is usually well tolerated and significant clinical adverse effects have been reported infrequently. The risk of hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) with MODURETIC is about 1-2 percent in patients without renal impairment or diabetes mellitus (see WARNINGS). Minor adverse reactions to amiloride HCl have been reported relatively frequently (about 20%) but the relationship of many of the reports to amiloride HCl is uncertain and the overall frequency was similar in hydrochlorothiazide treated groups. Nausea/anorexia, abdominal

pain, flatulence, and mild skin rash have been reported and probably are related to amiloride. Other adverse experiences 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 adverse reactions for MODURETIC listed in the following table have been arranged into two groups: (1) incidence greater than one percent, and (2) incidence one percent or less. The incidence for group (1) was determined from clinical studies conducted in the United States (607 patients treated with MODURETIC). The adverse effects listed in group (2) include reports from the same clinical studies and voluntary reports since marketing. The probability of a causal relationship exists between MODURETIC and these adverse reactions, some of which have been reported only *rarely*.

Incidence >1%	*Incidence ≤1%*
Body as a Whole	
Headache**	Malaise
Weakness**	Chest pain
Fatigue/tiredness	Back pain
	Syncope
Cardiovascular	
Arrhythmia	Tachycardia
	Digitalis toxicity
	Orthostatic hypotension
	Angina pectoris
Digestive	
Nausea/anorexia**	Constipation
Diarrhea	GI bleeding
Gastrointestinal pain	GI disturbance
Abdominal pain	Appetite changes
	Abdominal fullness
	Hiccups
	Thirst
	Vomiting
	Anorexia
	Flatulence
Metabolic	
Elevated serum potassium levels (>5.5 mEq per liter)***	Gout
	Dehydration
	Symptomatic hyponatremia†
Musculoskeletal	
Leg ache	Muscle cramps/spasm
	Joint pain
Nervous	
Dizziness**	Paresthesia/numbness
	Stupor
	Vertigo
Psychiatric	
None	Insomnia
	Nervousness
	Depression
	Sleepiness
	Mental confusion
Respiratory	
Dyspnea	None
Skin	
Rash**	Flushing
Pruritus	Diaphoresis
	Erythema multiforme including Stevens-Johnson syndrome
	Exfoliative dermatitis including toxic epidermal necrolysis
	Alopecia
Special Senses	
None	Bad taste
	Visual disturbance
	Nasal congestion
Urogenital	
None	Impotence
	Nocturia
	Dysuria
	Incontinence
	Renal dysfunction including renal failure
	Gynecomastia

**Reactions occurring in 3% to 8% of patients treated with MODURETIC (Those reactions occurring in less than 3% of the patients are unmarked.)

***See WARNINGS

†See PRECAUTIONS

Other adverse reactions that have been reported with the *individual components* and within each category are listed in order of decreasing severity.

Amiloride — Body as a Whole: Painful extremities, neck/shoulder ache, fatigability; *Cardiovascular*: Palpitation; *Digestive*: Activation of probable pre-existing peptic ulcer, abnormal liver function, jaundice, dyspepsia, heartburn; *Hematologic*: Aplastic anemia, neutropenia; *Integumentary*: Alopecia, itching, dry mouth; *Nervous System/Psychiatric*: Encephalopathy, tremors, decreased libido; *Respiratory*: Shortness of breath, cough; *Special Senses*: Increased intraocular pressure, tinnitus; *Urogenital*: Bladder spasms, polyuria, urinary frequency.

Hydrochlorothiazide — Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation; *Hematologic*: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity*: Anaphylactic reactions, necrotizing angiitis (vasculitis, cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, purpura; *Metabolic*: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia; *Nervous System/Psychiatric*: Restlessness; *Special Senses*: Transient blurred vision, xanthopsia; *Urogenital*: Interstitial nephritis (see WARNINGS).

OVERDOSAGE

No data are available in 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 HCl (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 also been administered, hypokalemia may accentuate cardiac arrhythmias.

DOSAGE AND ADMINISTRATION

MODURETIC should be administered with food.

The usual starting dosage is 1 tablet a day. The dosage may be increased to 2 tablets a day, if necessary. More than 2 tablets of MODURETIC daily usually are not needed and there is no controlled experience with such doses. *Hydrochlorothiazide can be given at doses of 12.5 to 50 mg per day* when used alone. Patients usually do not require doses of hydrochlorothiazide in excess of 50 mg daily when combined with other antihypertensive agents.

The daily dose is usually given as a single dose but may be given in divided doses. Once an initial diuresis has been achieved, dosage adjustment may be necessary. Maintenance therapy may be on an intermittent basis.

HOW SUPPLIED

No. 3385 — Tablets MODURETIC are peach-colored, *diamond-shaped, scored, compressed tablets, coded* MSD 917 on one side and M on the other. Each tablet contains 5 mg of anhydrous amiloride HCl and 50 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0917-68 in bottles of 100.

Storage

Keep container tightly closed. Protect from light, moisture, freezing. -20°C (-4°F) and store at room temperature, 15-30°C (59-86°F).

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MODURETIC® (Amiloride HCl-Hydrochlorothiazide)