Amiloride HCl Tablets, USP
Rx Only

DESCRIPTION
Amiloride HCl, an antikaliuretic diuretic agent, is a pyrazido-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 the salt of 3,5-diamino-6-chloro-pyrazine-carbonyl-guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. Its empirical formula is C_{14}H_{16}ClN_{4}O•HCl•2H_{2}O and its molecular weight is 348.87. Amiloride HCl is designated chemically as 3,5-diamino-6-chloro-pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 362.12. The empirical formula is C_{14}H_{16}ClN_{4}O•HCl•2H_{2}O and its structural formula is:

\[
\text{HCl} \quad \text{NH}_2 \quad \text{N} \quad \text{NH}_2 \quad \text{HCl} \quad 2\text{H}_2\text{O}
\]

Amiloride HCl is available for oral use as tablets containing 5 mg of amiloride hydrochloride. Each tablet contains the following inactive ingredients: calcium phosphate, lactose, magnesium stearate and starch.

CLINICAL PHARMACOLOGY
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. When administered with a thiazide or loop diuretic, amiloride HCl has been shown to decrease the elevated urinary excretion of magnesium which occurs when a thiazide or loop diuretic is given alone. Amiloride HCl has potassium-conserving activity in patients receiving thiazide-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 positive potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism action occurs 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. Amiloride HCl should be used alone when persistent hypokalemia has been documented and only with careful titration of the dose and close monitoring of serum electrolytes.

CONTRAINDICATIONS
Amiloride HCl should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq/liter).

Antikaliuretic Therapy or Potassium Supplementation Amiloride HCl should not be given to patients receiving potassiuum-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 amiloride HCl 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
Hypokalemia associated with chronic renal insufficiency, and evidence of diabetic nephropathy are contraindications to the use of amiloride HCl. 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 hypokalemia.

Hypersensitivity
Amiloride HCl is contraindicated in patients who are hypersensitive to this product.

WARNINGS
Hyperkalemia
Like other potassium-conserving agents, amiloride HCl may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly for 5 to 10% of patients in a large clinical trial comparing amiloride with a thiazide diuretic. This incidence is greater in patients with renal insufficiency (5.5-6.5 mEq/liter) compared to those who had hepatic cirrhosis (6.5-7.5 mEq/liter) or metabolic alkalosis, or those with resistant azotemia. Therefore, when amiloride HCl 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, amiloride HCl should not be used.

PRECAUTIONS
Cerebral
Electrolyte Imbalance and BUN Increase
Hypokalemia and hyperkalemia may occur when amiloride HCl 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 severely ill hospitalized patients. Potassium levels should be monitored carefully when amiloride HCl is used with other antikaliuretics or diuretics. This incidence is increased in patients with renal impairment and may result in the rapid development of hyperkalemia. When given 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 dose adjustment, and during any illness that could affect renal function.

The risk of hyperkalemia may be increased when potassium-conserving agents, including amiloride HCl, are administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, cyclosporine or tacrolimus. (See PRECAUTIONS, Drug Interactions). Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, facial 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 the baseline. There may also be lowering of the R wave and increased depth of the S wave, widening and flattening of the ST segment, and progressive widening of the QRS complex, prolongation of the PR interval, and development of complete heart block.

Treatment of hyperkalemia: If hyperkalemia occurs in patients taking amiloride HCl, the drug should be discontinued. Administration of the serum potassium level excesses 6.5 mEq/liter, active measures should be taken to reduce it. Such measures include the intravenous administration of a potassium antagonistic agent, such as sodium polystyrene sulfonate or enemas. Patients with persistent hyperkalemia may require dialysis.

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, amiloride HCl should be used with caution, if possible, in diabetic patients. Serum electrolytes and renal function must be monitored frequently.

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

Metabolic or Respiratory Acidosis
Amiloride HCl should not be used concomitantly with an antikaliuretic diuretic or an angiotensin II receptor antagonist because such patients may have impaired renal function, increased serum potassium levels and an increased risk of hyperkalemia. If amiloride HCl is given to these patients, frequent monitoring of serum potassium levels is necessary before glucose tolerance testing.

Cardiovascular
Carcinogenicity, Mutagenicity, Impairment of Fertility
There was no evidence of a tumorigenic effect when amiloride HCl was administered for 52 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 mg/kg/day (18 times the maximum daily human dose) and showed no evidence of carcinogenicity. Ames test, Salmonella typhimurium and in vivo mouse micronucleus test showed no evidence of mutagenicity. Impairment of fertility: There were no significant effects on fertility parameters but a low incidence of pup growth and survival occurred.

Drug Interactions
When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hyperkalemia, they should be used with caution and with frequent monitoring of serum potassium levels. (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 amiloride HCl is given with other diuretics, including non-steroidal anti-inflammatory agents, the drug should be used cautiously. Treatment with diuretics, including non-steroidal anti-inflammatory agents, can reduce the diuretic, natriuretic, and antihypertensive activity of amiloride HCl, even in patients without evidence of diabetic nephropathy. Therefore, amiloride HCl should be used with caution, if possible, in diabetic patients. Serum electrolytes and renal function must be monitored frequently.

In some patients, the administration of an anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when amiloride HCl is given with other diuretics, including non-steroidal anti-inflammatory agents, the drug should be used cautiously. Treatment with diuretics, including non-steroidal anti-inflammatory agents, can reduce the diuretic, natriuretic, and antihypertensive activity of amiloride HCl, even in patients without evidence of diabetic nephropathy. Therefore, amiloride HCl should be used with caution, if possible, in diabetic patients. Serum electrolytes and renal function must be monitored frequently.

Non-steroidal anti-inflammatory agents can reduce the diuretic, natriuretic and antihypertensive activity of amiloride HCl, even in patients without evidence of diabetic nephropathy. Therefore, amiloride HCl should be used with caution, if possible, in diabetic patients. Serum electrolytes and renal function must be monitored frequently.

Amiloride HCl should not be given to patients receiving a non-steroidal anti-inflammatory agent and a potassium-conserving diuretic. This incidence is greater in patients with renal impairment.

Since the use of indomethacin and potassium-sparing diuretics, such as amiloride HCl 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.

Drug Interactions
Amiloride HCl should not be administered concomitantly with an antikaliuretic diuretic or an angiotensin II receptor antagonist, cyclosporine or tacrolimus. (See PRECAUTIONS, Drug Interactions).
ADVERSE REACTIONS

Amiloride HCl 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, abdominal pain, fatigue, 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 diuretics, or with the underlying disease being treated.

The adverse reactions for amiloride HCl listed in the following table have been reported in 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 amiloride HCl). 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 amiloride HCl and these adverse reactions, some of which have been reported only rarely.

OVERDOSAGE

No data are available in regard to overdosage in humans. The oral LD₅₀ 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. 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 amiloride HCl should be discontinued and the patient observed closely. There is no specific antidote. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive. If hyperkalemia occurs, adequate measures should be taken to reduce the serum potassium levels.

WARNING

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 amiloride HCl 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 amiloride HCl, 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 amiloride HCl 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 renal function, or with the underlying disease, and the need for amiloride HCl should be administered with food.

Geriatric Use

Amiloride HCl should not be administered with food. Amiloride HCl, one 5 mg tablet daily, should be added to the usual antihypertensive or diuretic dosage of a kaliuretic diuretic. This dosage may be increased to 10 mg per day, if necessary. More than two 5 mg tablets of amiloride HCl daily are usually not needed, and there is limited clinical experience with such doses. If persistent hyperkalemia 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 amiloride HCl should be re-evaluated. Dosage adjustment may be necessary. Maintenance therapy may be on an intermittent basis.

If it is necessary to use amiloride HCl 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 hyperkalemia is documented with 10 mg, the dose can be increased to 15 mg, then 20 mg, with careful monitoring of electrolytes.

HOW SUPPLIED

Amiloride HCl Tablets, 5 mg, are off-white to light yellow, diamond-shaped, compressed tablets, embossed with “P291.” They are supplied in bottles of 100 (NDC 0574-0292-01).

STORAGE

Protect from moisture, freezing and excessive heat. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Manufactured By

Minneapolis, MN 55427
2100163
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* Reactions occurring in 3% to 8% of patients treated with amiloride HCl. (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 as serve as alerting information to physicians.

Activation of probable pre-existing peptic ulcer

Aplastic anemia

Neutropenia

Abnormal liver function