Product Monograph

Including Patient Medication Information

Pr MIDAMOR®

amiloride hydrochloride tablets

For oral use

5 mg of amiloride hydrochloride

USP

Antikaliuretic Agent with Diuretic Properties

AA Pharma Inc.

1165 Creditstone Road Unit #1
Vaughan, Ontario
M9L 1T9

Date of Authorization:
2025-06-10

Control Number: 292158

Recent Major Label Changes

7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics	2025-06

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

MIDAMOR (amiloride hydrochloride tablets) is indicated:

- For use alone or concomitantly with thiazide diuretics or other kaliuretic-diuretic agents in the treatment of patients with cirrhosis of the liver with ascites and edema.
- As an adjunct to thiazide diuretics or other kaliuretic-diuretic agents for the treatment of edema of cardiac origin or of hypertension in patients who have hypokalemia, or in whom maintenance of normal serum potassium levels is considered to be clinically important, e.g., 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

MIDAMOR used alone may provide satisfactory diuresis with diminished potassium loss and with a reduced risk of metabolic alkalosis. In resistant cases MIDAMOR 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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

1.2. Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hyperkalemia, 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia and 9.4 Drug-Drug Interactions, Non-steroidal anti-inflammatory drugs (NSAIDs).

2. Contraindications

MIDAMOR is contraindicated in the following conditions:

- **Hypersensitivity**: Patients with known hypersensitivity to amiloride or other derivatives, or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- **Hyperkalemia:** MIDAMOR should not be used in the presence of elevated serum potassium levels. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia.
- **Antikaliuretic Therapy or Potassium Salts:** Other antikaliuretic agents and potassium supplements are contraindicated in patients receiving amiloride hydrochloride (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 MIDAMOR. See 7 WARNINGS AND PRECAUTIONS, Renal.

3. Serious Warnings and Precautions Box

Hyperkalemia

- Hyperkalemia (i.e., serum potassium levels over 5.5 mEq/L), has been observed in patients who received amiloride hydrochloride tablets 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, patients 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 (See 7 Warnings and Precautions, Hyperkalemia).

4. Dosage and Administration

4.1. Dosing Considerations

- The incidence of hyperkalemia is dose-related and this should be considered especially when daily doses over 10 mg are used.
- Patients 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.

4.2. Recommended Dose and Dosage Adjustment

Hepatic Cirrhosis with Ascites and Edema

Treatment should be started with a small dose of MIDAMOR, i.e., one 5 mg tablet daily, plus a small dose of a diuretic agent (other than antikaliuretics). If necessary, dosages of both drugs may be increased gradually until effective diuresis is obtained. The dosage of MIDAMOR should not exceed four tablets (20 mg) a day. 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.

In those instances where MIDAMOR is used alone, the initial daily dosage should be two 5 mg tablets (as a single dose or one tablet twice a day). Dosage may be increased depending on the need. The total daily dosage should not exceed four tablets (20 mg). After diuresis has been achieved the dosage may be reduced by decrements of one tablet to the least amount required.

Edema of Cardiac Origin

MIDAMOR, one or two 5 mg tablets daily, may be given with the usual doses of a diuretic agent (other than antikaliuretics). This dose is sufficient in most cases. If potassium levels remain low, the dosage of MIDAMOR may be increased gradually. The dosage of MIDAMOR should not exceed four tablets (20 mg) a day.

The optimal dosage is determined by the serum potassium level. Reduction in dosage should be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

Hypertension

MIDAMOR, one or two 5 mg tablets daily, is given with the usual antihypertensive dosage of a diuretic agent (other than antikaliuretics). The dosage may be adjusted if necessary. More than two 5 mg tablets of MIDAMOR daily usually is not needed; in any event, the maximum dosage is four tablets (20 mg) a day.

Pediatrics

Health Canada has not authorized an indication for pediatric use.

4.5. Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5. Overdose

No data are available in regard to overdosage in humans.

It is not known whether the drug is dialyzable.

If hyperkalemia occurs, active measures should be taken to reduce the serum potassium levels. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia.

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 antidote. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 5 mg	Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

MIDAMOR 5 mg tablets: each yellow, diamond-shaped, biconvex tablet, engraved "5" on one side and plain on the other, contains 5 mg of amiloride hydrochloride. Available in bottles of 100 tablets.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

Driving and Operating Machinery

The effect of MIDAMOR on ability to drive and operate machinery has not been studied. However, since its use has been associated with dizziness, weakness, visual disturbances, vertigo, orthostatic hypotension and somnolence, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination if they are experiencing any of these effects. See 8 Adverse Reactions.

Endocrine and Metabolism

Hyperkalemia:

The risk of hyperkalemia may be increased when potassium-conserving agents, including amiloride hydrochloride, are administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, cyclosporine or tacrolimus (see 9.4 Drug-Drug Interactions, Angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus).

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.

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 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 MIDAMOR 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, MIDAMOR should be discontinued at least 3 days before glucose tolerance testing.

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 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.

Hepatic/Biliary/Pancreatic

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 a few cirrhotic patients, pre-existing jaundice increased, but the relationship to drug is uncertain.

Monitoring and Laboratory Tests

Electrolyte Imbalance and BUN Increases: Hyponatremia and hypochloremia may occur when MIDAMOR is used with other diuretics. 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, careful monitoring of serum electrolytes and BUN levels is important when using MIDAMOR.

Renal

Impaired Renal Function: Patients with impaired renal function other than those listed under CONTRAINDICATIONS (see 2 CONTRAINDICATIONS) and who have BUN levels over 30 mg per 100 mL, serum creatinine levels over 1.5 mg per 100 mL, or with whole blood urea values over 60 mg per 100 mL or with diabetes mellitus, should not receive the drug without careful, frequent monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of amiloride hydrochloride 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.

Reproductive Health

- **Fertility**

  Reproduction studies in rats showed no evidence of impaired fertility (see 16 Non-Clinical Toxicology - Reproductive and Developmental Toxicology.

7.1 Special Populations

7.1.1 Pregnant Women

Teratologic studies with amiloride hydrochloride in rabbits and mice revealed no evidence of harm to the fetus. 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.

Because clinical experience is limited, MIDAMOR is not recommended for use during pregnancy. The potential benefits of the drug must be weighed against possible hazards to the fetus if it is administered to a woman of childbearing age.

7.1.2 Breastfeeding

It is not known whether MIDAMOR is excreted in human milk. In rats secretion of amiloride hydrochloride in milk has been demonstrated. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

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 and potassium levels. 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. In general, dose selection for an elderly patient should start 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.

Clinical studies of amiloride hydrochloride 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.

See 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Renal See 3 SERIOUS WARNINGS AND PRECAUTIONS, Hyperkalemia; 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia and 9.4 Drug-Drug Interactions, Non-steroidal anti-inflammatory drugs (NSAIDs).

8 Adverse Reactions

8.1 Adverse Reaction Overview

While rare, the most serious adverse effect of amiloride hydrochloride is symptomatic hyperkalemia (symptoms of hyperkalemia may include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock and ECG abnormalities). See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug.

The following incidence of adverse reactions was determined from clinical trials (837 patients treated with amiloride hydrochloride).

Table 2 - Adverse Reactions Reported from Clinical Trials Occurring in ≥ 1% of Patients

System organ class/preferred term	Amiloride hydrochloride n = 837 (%)
Gastrointestinal disorders	
Nausea/anorexia	6.1
Diarrhea	3.8
Vomiting	3.3
Abdominal pain	<3%
Gas pain	<3%
Appetite changes	<3%
Constipation	<3%
General disorders and administration site conditions	
Weakness	<3%
Fatigability	<3%
Musculoskeletal and connective tissue disorders	
Muscle cramps	<3%
Metabolism and nutrition disorders	
Asymptomatic hyperkalemia	8.0
Nervous system disorders	
Headache	7.6
Dizziness	<3%
Encephalopathy	<3%
Reproductive system and breast disorders	
Impotence	<3%
Respiratory, thoracic, and mediastinal disorders	
Cough	<3%
Dyspnea	<3%

8.3. Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Aplastic anemia, neutropenia

Cardiac disorders: Angina pectoris, Arrhythmia, Palpitation, Complete heart block (in a patient with a partial heart block)

Eye disorders : Visual disturbances

Gastrointestinal disorders : Activation of probable pre-existing peptic ulcer, Gastrointestinal bleeding, Abdominal fullness, Gastrointestinal disturbance, Thirst, Heartburn, Flatulence, Dyspepsia, Dryness of the mouth

General disorders and administration site conditions: Chest pain

Hepatobiliary disorders: Jaundice
In cirrhotic patients, jaundice associated with the underlying disease process has deepened in a few instances, but the relationship to drug is uncertain.

In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, coma, and increased jaundice, have been reported in association with diuretics, including amiloride hydrochloride.

Investigations: Abnormalities of liver function tests, Increased intraocular pressure

Metabolism and nutrition disorders: Hyperuricemia, Symptomatic hyperkalemia, Hyponatremia

Musculoskeletal and connective tissue disorders: Joint pain, Leg ache, Back pain, Neck/shoulder ache, Pain extremities

Nervous System disorders: Paresthesia, Tremors, Vertigo, Mental confusion, Insomnia, Somnolence, Tinnitus

Pyschiatric disorders: Nervousness, Decreased libido, Depression

Renal and urinary disorders: Polyuria, Dysuria, Urinary frequency, Bladder spasms

Respiratory, thoracic, and mediastinal disorders: Shortness of breath, Nasal congestion

Skin and subcutaneous tissue disorders: Skin rash, Pruritus, Alopecia

Vascular disorders: Orthostatic hypotension

8.5 Post-Market Adverse Reactions

During post-marketing experience with amiloride hydrochloride, gynecomastia and itching have been reported.

9 Drug Interactions

9.1. Serious Drug Interactions

Serious Drug Interactions
• **Antikaliuretic therapy or potassium salts**: Other antikaliuretic agents and potassium supplements are contraindicated in patients receiving amiloride hydrochloride. Such combination therapy is commonly associated with rapid increases in plasma potassium levels. • **Non-steroidal anti-inflammatory drugs (NSAIDs)**: Concomitant administration of NSAIDs and potassium-sparing agents, including amiloride hydrochloride, may cause hyperkalemia and renal failure, particularly in elderly patients.

9.3. Drug-Behaviour Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Lithium	T	Diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Lithium should generally not be given with diuretics.
Angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus	T	When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased.	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.
Non-steroidal anti-inflammatory drugs (NSAIDs)	T	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. Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride hydrochloride, may cause hyperkalemia and renal failure, particularly in elderly patients.	When amiloride hydrochloride is used concomitantly with NSAIDs, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Renal function and serum potassium levels should be carefully monitored.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

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. Amiloride hydrochloride interferes with the mechanism involved in the exchange of sodium for potassium in the distal convoluted tubule and collecting duct of the nephron. An increase in sodium and a decrease in potassium and hydrogen ion excretion are induced in the presence or absence of aldosterone, thereby suggesting a direct tubular action of the drug. Chloride excretion may remain unchanged or increase slowly with continued therapy.

Amiloride hydrochloride is chemically unrelated to other known antikaliuretic or diuretic agents. It is a salt of a moderately strong base (pKa 8.7). When administered with hydrochlorothiazide, it has been shown to result in less excretion of magnesium than thiazide or loop diuretics used alone. An enzymatic basis for the renal action of amiloride hydrochloride has not been elucidated. It is not an inhibitor of carbonic anhydrase.

10.2 Pharmacodynamics

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.

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 in rats. Amiloride hydrochloride antagonizes the kaliuretic effect of the other diuretic.

10.3 Pharmacokinetics

Absorption

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.

Distribution

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

Metabolism

Amiloride hydrochloride is not metabolized by the liver.

Elimination

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.

Special Populations and Conditions

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia, 7.1.4 Geriatrics, and 9.4 Drug-Drug Interactions, Non-steroidal anti-inflammatory drugs (NSAIDs).
- **Pregnancy and Breast-feeding:** Amiloride hydrochloride is not recommended for use during pregnancy. See 7.1.1 Pregnant Women.

  It is unknown if amiloride hydrochloride is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. See 7.1.2 Breastfeeding.
- **Hepatic Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.
- **Renal Insufficiency:** Since MIDAMOR is mostly excreted by the kidneys, it is contraindicated in patients with anuria, acute renal failure, severe or progressive renal disease, and diabetic nephropathy (See 2 CONTRAINDICATIONS).

11 Storage, Stability, and Disposal

Store at room temperature (15°C to 30°C). Keep out of reach and sight of children.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

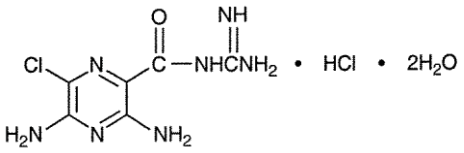
Proper name: Amiloride hydrochloride

Chemical names:

1) Pyrazinecarboxamide, 3,5-diamino-N-(amino-iminomethyl)-6- chloro-, monohydrochloride dihydrate;
2) N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide monohydrochloride dihydrate

Molecular formula and molecular mass: $C_6H_8ClN_7O.HCl.2H_2O$ and 302.12 g/mol

Structural formula:



Physicochemical properties: A yellow to greenish yellow, odourless or practically odourless, crystalline compound, soluble in water. Amiloride hydrochloride is chemically unrelated to other known antikaliuretic or diuretic agents. It is a salt of a moderately strong base (pKa 8.7).

14 Clinical Trials

14.2 Comparative Bioavailability Studies

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of amiloride hydrochloride was measured and compared following oral administration of MIDAMOR (additional formulation B) (1 x 5 mg) tablets or MIDAMOR (original formulation A) (1 x 5 mg) tablets. The results from measured data are summarized as follows:

Table 4 - Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data (Dose: 1 x 5 mg) From measured data			
Parameter	**Geometric Mean Arithmetic Mean (CV%)**		**Ratio of Geometric Means (%)****
	MIDAMOR (B)	**MIDAMOR (A) †**	
AUC_T (ng·hr/mL)	85.8 88.2 (23)	86.9 89.3 (21)	98.7
AUC_{0-72} (ng·hr/mL)	91.6 92.9 (17)	91.7 93.1 (17)	99.8
AUC_I (ng·hr/mL)	92.9 95.7 (23)	92.6 95.3 (22)	100.3
C_{max} (ng/mL)	5.45 5.57 (20)	5.46 5.56 (19)	99.9
T_{max} (hr)*	3.92 (25)	3.86 (27)	-
$t_{1/2}$ (hr)*	20.4 (47)	17.4 (25)	-
* Arithmetic means (CV%). ** Based on the least squares estimate. † Midamor, marketed by Merck Frosst, purchased in Canada.			

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General Toxicology

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. A no observed adverse effect level (NOAEL) of 5 mg/kg is approximately equivalent to a dose 2 times greater than the maximum human recommended dose of 20 mg/day, considering a human body weight of 50 kg.

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 adrenals was observed in all treated dogs. Due to effects seen at every dose, no safety margin was derived.

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. A NOAEL of 2 mg/kg is approximately equivalent to a dose 1.6 times greater than the maximum human recommended dose of 20 mg/day.

Carcinogenicity

Amiloride hydrochloride had no apparent carcinogenic effect in albino mice treated with oral doses up to 10 mg/kg/day for 92 weeks or in rats treated with oral doses up to 8 mg/kg/day for 104 weeks. These strains of rats and mice have been shown to be susceptible to the activity of a known carcinogen. In mice, this represents a safety margin of 2-fold and in rats, of 3-fold.

Genotoxicity

Amiloride hydrochloride did not have any mutagenic activity in the Ames microbial mutagen assay with or without rat liver activation systems.

Reproductive and Developmental Toxicology

Amiloride hydrochloride had no teratogenic effect by external, visceral, or skeletal examination of the progeny of albino New Zealand rabbits treated orally with 2, 4, or 8 mg/kg/day (base) on days 6 through 18 of gestation or CF_1 albino mice treated orally with 2.5, 5.0 or 10.0 mg/kg/day (base) on days 6 through 15 of gestation. In rabbits the highest dose caused definite maternal weight loss; in mice 10 mg/kg/day was toxic (6 of 19 died). These results yield a maternal safety margin of 3-fold and a developmental safety margin of 6-fold in rabbits, and a safe dose approximately equivalent to the maximum human recommended dose in mice.

No effect on reproductive performance or fertility in albino rats (GOBS strain) given 2, 4 or 8 mg/kg/day (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. A NOAEL of 4 mg/kg is approximately equivalent to a dose 1.6 times greater than the maximum human recommended dose of 20 mg/day.

Special Toxicology

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 a chronic study in dogs.

Juvenile Toxicity

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]MIDAMOR®

amiloride hydrochloride tablets

This Patient Medication Information is written for the person who will be taking **MIDAMOR**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **MIDAMOR**, talk to a healthcare professional.

Serious warnings and precautions box

MIDAMOR may cause high levels of potassium in your blood (hyperkalemia) when taken alone or with diuretics. This may be more likely to happen if you:

- are 65 years of age or older,
- are diabetic,
- have liver, heart, or kidney problems,
- are already sick, or
- are receiving treatment with diuretics

Your healthcare professional will perform check-ups and tests to monitor the levels of potassium in your blood.

Talk to your healthcare professional right away if you have:

- numbness and tingling,
- muscles that feel weak,
- unusual tiredness,
- slow heart rate or
- shock.

What MIDAMOR is used for:

MIDAMOR is used:

- alone or with other diuretics to treat adults with liver disease who have swelling caused by a build-up of fluid in the belly (ascites) and in the tissues (edema).
- with other diuretics to treat:
    - swelling caused by a build up of fluid in the tissues due to heart problems or
    - high blood pressure (hypertension) in adults who have low levels of potassium in their blood (hypokalemia) or who need to maintain normal levels of potassium.

How MIDAMOR works:

MIDAMOR is a potassium conserving drug (antikaliuretic drug). It helps the body lose excess salt but keep a normal amount of potassium (an electrolyte) in the blood.

The ingredients in MIDAMOR are:

Medicinal ingredients: Amiloride hydrochloride

Non-medicinal ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and yellow ferric oxide.

MIDAMOR comes in the following dosage form(s):

Tablets: 5 mg

Do not use MIDAMOR if:

- you are allergic to amiloride hydrochloride or any of the other ingredients in MIDAMOR.
- you have high levels of potassium levels in the blood.
- you are taking any other potassium conserving drugs or potassium supplements.
- you have difficulty urinating or produce no urine (anuria).
- you have kidney failure, severe or
- you have worsening kidney disease or problems with your kidneys because of diabetes (diabetic nephropathy).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MIDAMOR. Talk about any health conditions or problems you may have, including if you:

- have diabetes.
- have liver, heart or kidney problems.
- have cardiopulmonary disease (disease involving both the lungs and heart).
- are taking other diuretics or “water pills”.
- have low sodium and chloride levels in your blood.
- have high blood urea nitrogen (BUN) levels.
- have high creatinine levels in blood.
- have lactose intolerance.
- are pregnant or planning to become pregnant.
- are breastfeeding.
- are 65 years of age or older.

Other warnings you should know about:

Pregnancy: It is not known if MIDAMOR can harm an unborn baby. Tell your healthcare professional if you are pregnant or think you may be pregnant before your treatment with MIDAMOR. You and your healthcare professional will decide if you should be given MIDAMOR during pregnancy.

Breastfeeding: It is not known if MIDAMOR passes into breast milk and may harm your baby. Your healthcare professional will decide if you should stop breastfeeding or stop taking MIDAMOR.

Check-ups and testing: While you are taking MIDAMOR, your healthcare professional will do check-ups and tests to monitor:

- the level of electrolytes (such as potassium), creatine and urea nitrogen in your blood
- acid-base balance
- health of your kidneys

Driving and using machines: MIDAMOR can cause low blood pressure, dizziness, weakness, sleepiness and problems with your vision. Do not drive a car or do other tasks that require special attention if you feel any of these effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Do not take MIDAMOR with:

- nonsteroidal anti-inflammatory drugs (NSAIDs) used to reduce pain and swelling, including ibuprofen, naproxen, and celecoxib.
- potassium sparing diuretics (a specific kind of "water pill" that makes your body keep potassium).
- potassium supplements.

Taking MIDAMOR with any of these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure you are taking these medicines.

The following may also interact with MIDAMOR:

- lithium used to treat bipolar disease.
- angiotensin-converting-enzyme inhibitors used to treat high blood pressure and heart failure.
- cyclosporine or tacrolimus used to suppress the body's immune response, or prevent organ transplant rejection.

How to take MIDAMOR:

- Take MIDAMOR exactly as your healthcare professional tells you. Talk to your healthcare professional if you are not sure.
- It is recommended to take your dose at the same time every day.

Usual dose:

Your healthcare professional will determine the dose that is right for you. Your dose will depend on how much potassium is in your blood and other diuretics you are taking.

To treat swelling in adults with liver disease: 1 tablet (5 mg) per day. Do not take more than 4 tablets (20 mg) in a day.

To treat swelling in adults with heart problems: 1 or 2 tablets per day or in divided doses. Do not take more than 4 tablets (20 mg) a day.

To treat high blood pressure in adults: 1 or 2 tablets per day or in divided doses. Do not take 4 tablets (20 mg) a day.

Overdose:

Signs of an overdose may include:

- dehydration
- electrolyte imbalance

If you think you, or a person you are caring for, have taken too much MIDAMOR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take MIDAMOR, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Do NOT take a double dose to make up for the missed dose.

Possible side effects from using MIDAMOR:

These are not all the possible side effects you may have when taking MIDAMOR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea
- loss or change in appetite
- diarrhea
- vomiting
- headache
- abdominal pain
- gas pain
- constipation
- weakness
- tiredness
- muscle cramps and pain
- dizziness or spinning sensation
- brain disease
- difficulty in getting and keeping an erection, change in libido
- cough
- shortness of breath
- dry mouth, thirst
- numbness and tingling
- hearing problems (ringing in the ears)
- confusion
- difficult sleeping (insomnia)
- drowsiness

- shakiness (tremors)
- nervousness
- stuffy nose
- problems with your vision

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Encephalopathy (disease or disorder of the brain): confusion or disorientation, trouble thinking, memory loss, changes in personality		√	
Hyperkalemia (high level of potassium in the blood): muscle weakness, abnormal or slow heart rhythms, significant tingling and muscle contraction, paralysis			√
Rare			
Dysuria: pain or burning sensation during urination		√	
Gastrointestinal (GI) bleeding: (bleeding anywhere along the GI tract between mouth and anus): blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness			√
Heart problems: fast or irregular heartbeat, palpitations, chest pain, difficulty breathing, fainting		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
Increased intraocular pressure (pressure in the eye)		√	
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, itching all over your body		√	
Musculoskeletal pain (pain that affects the muscles and tendons along with bones): muscle pain, limb pain, joint pain and bone pain	√		
Skin rash, itching, loss of hair	√		
Unknown			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Aplastic anemia (when cells meant to develop into mature blood cells are damaged): fatigue, weakness, pale skin		√	
Hyperuricemia (high uric acid levels in the blood): intense pain, joint stiffness, redness and swelling		√	
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		√	
Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		√	
Peptic ulcer: dull or burning stomach pain, heartburn, feeling of fullness or bloating, nausea		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about MIDAMOR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-

product-database.html); the manufacturer's website http://www.aapharma.ca/en/, or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

Date of Authorization: 2025-06-10