

# AMIZIDE

***Hydrochlorothiazide; amiloride hydrochloride***

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## Presentation

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Yellow, flat bevel-edged tablets, 11/32" diameter, imprinted AMIZIDE on one side. Each AMIZIDE tablet contains 5mg Amiloride HCL and 50mg Hydrochlorothiazide.

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## Uses

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### ***Actions***

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

AMIZIDE 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 AMIZIDE than with a thiazide or loop diuretic used alone.

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

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

*Hydrochlorothiazide:* Hydrochlorothiazide is an orally effective diuretic and antihypertensive.

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

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

Amiloride HCl usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours.

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

### ***Pharmacokinetics***

#### CLINICAL PHARMACOLOGY

Hydrochlorothiazide and amiloride tablets usually begin to act within 2 hours following administration. Its diuretic and natriuretic effects are maximal at about the fourth hour, and there is a detectable activity for approximately 24 hours. The effective diuretic action of the medicine, however, persists only for about 12 hours. The potassium retaining action of amiloride HCl is apparent within the first 2 hours after administration and reaches its peak activity at about the sixth to tenth hour following oral administration. The effective action of the medicine persists for at least 12 hours while there is detectable antikaliuretic activity for 24 hours.

*Amiloride HCl:* Amiloride HCl is a potassium-conserving (antikaliuretic) medicine 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 interferes with the mechanism involved in the exchange of sodium for potassium in the distal convoluted tubule and collecting duct of the nephron.

Amiloride HCl is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone, thereby suggesting a direct tubular action of the medicine.

Sodium excretion increases moderately, while chloride excretion may remain unchanged or increase slowly with continued therapy. This effect may diminish the risk of hypochloremic alkalosis encountered with some saluretic agents.

Potassium retention to the point of hyperkalaemia may be avoided by keeping the dosage of amiloride HCl below 20 mg per day. 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 metabolised 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 metabolised by the liver, medicine accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

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

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

The onset of the diuretic action of hydrochlorothiazide occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours. Hydrochlorothiazide is eliminated rapidly by the kidney.

The mechanism of the antihypertensive effect of thiazides may be related to the excretion and redistribution of body sodium. Hydrochlorothiazide usually does not cause clinically important changes in normal blood pressure.

## ***Indications***

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

AMIZIDE may be used alone or as an adjunct to other antihypertensive medicines in conditions such as:-

Hypertension

Oedema of cardiac origin

Hepatic cirrhosis with ascites and oedema

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## **Dosage and Administration**

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*AMIZIDE Tablets:* Each tablet contains 5 mg amiloride HCl and 50 mg hydrochlorothiazide.

The following dosage refers to the administration of tablets.

*Hypertension:* The usual dosage is one to two tablets of AMIZIDE given once a day or in divided doses. The dosage may be increased if necessary, but must not exceed four tablets of AMIZIDE a day.

*Oedema of Cardiac Origin:* AMIZIDE may be started at a dosage of 1 or 2 tablets a day. Dosage may be increased if necessary but must not exceed 4 tablets a day. The optimal dosage is determined by the diuretic response and the serum potassium level. Once an initial diuresis has been achieved, reduction in dosage should be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

*Hepatic Cirrhosis with Ascites:* (See Warnings and Precautions).

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

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

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## Contraindications

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Hyperkalaemia (defined as > 5.5 mEq/l).

Other concomitant antidiuretic therapy or potassium supplementation (see Warnings and Precautions).

Renal insufficiency (anuria, acute renal failure, severe progressive renal disease, and diabetic nephropathy (see also Warnings and Precautions)).

Hypersensitivity to any component of this product or other sulfonamide-derived medicines.

(See also Use in Pregnancy, Nursing Mothers and Pediatric Use under Warnings and Precautions).

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## Warnings and Precautions

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

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

*Treatment of Hyperkalaemia:* Should hyperkalaemia occur in patients taking AMIZIDE, the medicine should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

*Impaired Renal Function:* When creatinine clearance falls below 30 ml/min thiazide diuretics are ineffective.

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

*Electrolyte Imbalance:* Although the likelihood of electrolyte imbalance is lessened with AMIZIDE, careful check should be kept for signs of fluid and electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, hypokalemia and hypomagnesemia. It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids.

Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with hydrochlorothiazide as with any other potent diuretic, especially with brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (eg. increased ventricular irritability).

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

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

*Hepatic Disease:* Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

*Metabolic:* Hyperuricaemia may occur or gout may be precipitated in certain patients receiving thiazide therapy.

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

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

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

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

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

*Use in Pregnancy:* The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated and exposes mother and fetus to unnecessary hazard. Diuretics do not

prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

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

*Nursing Mothers:* Thiazides appear in breast milk. If use of the medicine is deemed essential, the patient should stop nursing.

*Paediatric Use:* The use of amiloride HCl in children has not been established; therefore, AMIZIDE is not recommended in the pediatric age group.

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## Adverse Effects

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AMIZIDE is usually well tolerated. Although minor side effects have been reported relatively frequently, significant side effects have been reported infrequently. Side effects that have been reported with hydrochlorothiazide/amiloride tablets 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.

### *Body as a whole:*

headache\*

weakness\*

fatigue

malaise

chest pain

back pain

syncope

### *Cardiovascular:*

arrhythmia

tachycardia

digitalis toxicity

orthostatic hypotension

angina pectoris

### *Digestive:*

nausea/anorexia\*

vomiting

diarrhoea

constipation

abdominal pain

GI bleeding

appetite changes

abdominal fullness

flatulence

thirst

hiccups

*Metabolic:*

elevated serum potassium levels (> 5.5 mEq per litre)

electrolyte imbalance

hyponatraemia

gout

dehydration

symptomatic hyponatraemia

*Integumentary:*

rash\*

pruritus

flushing

diaphoresis

*Musculoskeletal:*

leg ache

muscle cramps

joint pain

*Nervous:*

dizziness\*

vertigo

paraesthesia

stupor

*Psychiatric:*

insomnia

nervousness

mental confusion

depression

sleepiness

*Respiratory:*

dyspnoea

*Special Senses:*

bad taste

visual disturbance

nasal congestion

*Urogenital:*

impotence

dysuria

nocturia

incontinence

renal dysfunction including renal failure

\* Side effects that have been reported most frequently during controlled clinical trials with hydrochlorothiazide/amiloride tablets. Other side effects that have been reported with the individual components are listed below:-

AMILORIDE

*Body as a whole:*

neck/shoulder ache

pain in extremities

*Digestive:*

abnormal liver function

activation of probable pre-existing peptic ulcer

dyspepsia

jaundice

*Integumentary:*

dry mouth

alopecia

diaphoresis

*Nervous:*

tremors

encephalopathy

*Haematologic:*

aplastic anaemia

neutropenia

*Cardiovascular:*

one patient with partial heart block developed complete heart block

palpitation

*Psychiatric:*

decreased libido

somnolence

*Respiratory:*

cough

*Special Senses:*

tinnitus

increased intraocular pressure

*Urogenital:*

polyuria

urinary frequency

bladder spasm

HYDROCHLOROTHIAZIDE

*Body as a whole:*

anaphylactic reaction

fever

*Cardiovascular:*

necrotizing angitis (vasculitis, cutaneous vasculitis)

*Digestive:*

jaundice (intrahepatic cholestatic jaundice)

pancreatitis

cramping

gastric irritation

*Endocrine/Metabolic:*

glycosuria

hyperglycaemia

hyperuricaemia

*Integumentary:*

photosensitivity

sialadenitis

urticaria

*Psychiatric:*

restlessness

*Renal:*

interstitial nephritis

*Respiratory:*

respiratory distress including pneumonitis and pulmonary oedema

*Special Senses:*

transient blurred vision

xanthopsia

*Haematologic:*

agranulocytosis

aplastic anaemia

hemolytic anaemia

leukopenia

purpura

thrombocytopenia

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## **Interactions**

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When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, the risk of hyperkalaemia 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.

*Thiazide Diuretics:* When given concurrently the following medicines may interact with thiazide diuretics.

*Alcohol, Barbiturates, or Narcotics:* Potentiation of orthostatic hypotension may occur.

*Antidiabetic Medicines:* (Oral agents and insulin) – dosage adjustment of the antidiabetic medicine may be required.

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

*Corticosteroids, Acth:* Intensified electrolyte depletion, particularly hypokalaemia.

*Pressor Amines(eg. Norepinephrine):* Possible decreased response to pressor amines but not sufficient to preclude their use.

*Skeletal Muscle Relaxants, Nondepolarizing (eg. 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 inserts for lithium preparations before use of such preparations.

*Nonsteroidal Anti-Inflammatory Medicines:* In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of diuretics.

*Medicine/Laboratory Test Interactions:* Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see Warnings and Precautions).

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## Overdosage

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No data are available with regard to overdosage in humans. The oral LD<sub>50</sub> of the combination medicine is 189 and 422 mg/kg for female mice and female rats, respectively. It is not known whether the medicine is dialyzable.

No specific information is available on the treatment of overdosage with hydrochlorothiazide and amiloride tablets, and no specific antidote is available. Treatment is symptomatic and supportive. Therapy with AMIZIDE 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<sub>50</sub> of amiloride hydrochloride (calculated as the base) is 56 mg/kg in mice and 36 to 85 mg/kg in rats, depending on the strain.

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

*Hydrochlorothiazide:* The oral LD<sub>50</sub> of hydrochlorothiazide is greater than 10.0 g/kg in both mice and rats.

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has been administered, hypokalemia may accentuate cardiac arrhythmias.

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## **Pharmaceutical Precautions**

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Store below 25°C.

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## **Medicine Classification**

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Prescription Medicine.

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## **Package Quantities**

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Tablets available in bottles of 100 and 500.

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## **Further Information**

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Nil.

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## **Name and Address**

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Mylan New Zealand Limited  
PO Box 11-183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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## **Date of Preparation**

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2 February 2009