

# Amizide

Hydrochlorothiazide and Amiloride hydrochloride



## PRODUCT INFORMATION

### NAME OF THE MEDICINE

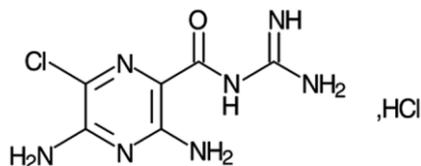
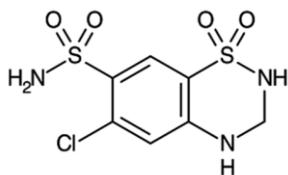
Active ingredients: Hydrochlorothiazide

Amiloride hydrochloride

Chemical names: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulphonamide 1,1-dioxide

3,5-diamino-N-carbamimidoyl-6-chloropyrazine-2-carboxamide

Structural formulas:



Molecular formulas:  $C_7H_8ClN_3O_4S_2$

$C_6H_9Cl_2N_7O, 2H_2O$

Molecular weights: 297.7

302.1

CAS Registry Nos: 58-93-5

17440-83-4

### DESCRIPTION

Hydrochlorothiazide is a white or almost white, odourless, crystalline powder with a slightly bitter taste. It is very slightly soluble in water, sparingly soluble in ethanol (96%) and soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

Amiloride hydrochloride is a pyrazinecarbonylguanidine that is unrelated chemically to other known diuretic or antihypertensive agents. It is not acidic like the thiazides, but is the salt of a moderately strong base, amiloride, pKa 8.7.

Amiloride hydrochloride is a pale yellow to greenish-yellow, almost odourless powder. It is slightly soluble in water and ethanol (96%), and practically insoluble in chloroform and in ether.

Amizide tablets contain 50 mg hydrochlorothiazide and 5 mg amiloride hydrochloride. The tablets also contain the following inactive ingredients: lactose, starch – wheat, povidone, sodium starch glycolate, magnesium stearate.

### PHARMACOLOGY

Amizide combines the potassium-conserving action of amiloride hydrochloride with the natriuretic action of hydrochlorothiazide.

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

*Amiloride hydrochloride* is a potassium-conserving (antihypertensive) drug that possesses weak (compared to the thiazide diuretics) natriuretic, diuretic and antihypertensive activity. These effects have been partially additive to the

effects of thiazide diuretics in some clinical studies. Amiloride hydrochloride has potassium-conserving activity in patients receiving kaliuretic-diuretic agents.

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

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

*Hydrochlorothiazide.* The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide does not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases the 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 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

## Pharmacokinetics

*Amiloride hydrochloride.* . Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Amiloride hydrochloride is not metabolised by the liver but is excreted unchanged by the kidneys. About 50% of a 20 mg dose of amiloride hydrochloride is excreted in the urine and 40% in the stool within 72 hours. Amiloride hydrochloride has little effect on glomerular filtration rate or renal blood flow. Because amiloride hydrochloride is not metabolised by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

*Hydrochlorothiazide.* Hydrochlorothiazide is not metabolised 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% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placenta but not the blood-brain barrier and is excreted in breast milk.

## INDICATIONS

Amizide is indicated in the treatment of patients with:

- oedema of cardiac origin;
- hepatic cirrhosis with ascites;
- hypertension in whom potassium depletion might be anticipated.

Amizide, with its combination of amiloride hydrochloride and hydrochlorothiazide, minimises the possibility of the development of excessive potassium loss in patients during vigorous diuresis for prolonged periods. Amizide, with its built in potassium sparing agent, is especially indicated in those conditions where the positive effect on potassium balance is particularly important.

*Hypertension.* Amizide may be used alone or as an adjunct to other anti-hypertensive drugs. Since it enhances the action of these agents, the dosage of these antihypertensive drugs may need to be reduced to avoid the risk of an excessive drop in blood pressure.

## CONTRAINDICATIONS

*Impaired Renal Function.* Amizide is contraindicated in cases of acute renal failure, diabetic nephropathy, anuria and severe progressive renal disease. Patients with increases in blood urea nitrogen (BUN) over 10.7 mmol/L, in serum creatinine levels over 0.13 mmol/L, or in whole blood urea values over 10.0 mmol/L should not be given the drug without careful, frequent monitoring of serum electrolytes and BUN levels. In the presence of renal impairment, potassium retention is accentuated by the addition of an anti-kaliuretic agent and may result in the rapid development of hyperkalaemia.

*Hyperkalaemia.* Amizide should not be used in the presence of elevated plasma potassium levels (interpreted as over 5.5 mmol/L).

*Antikaliuretic Therapy or Potassium Supplementation.* Other antikaliuretic agents and potassium supplements or a potassium-rich diet are contraindicated in patients receiving Amizide; such combination therapy is commonly associated with rapid increases in plasma potassium levels.

*Known sensitivity to the drug.* Amizide is contraindicated in patients who are hypersensitive to this product, or to other sulfonamide derived drugs.

*Use in Children.* The safety for use of amiloride hydrochloride in children has not been established, therefore Amizide is not recommended in the paediatric age group. (see also **Use in Pregnancy** and **Use in Lactation**).

## PRECAUTIONS

*Diabetes Mellitus.* In diabetic patients, hyperkalaemia has commonly occurred during therapy with amiloride hydrochloride, particularly if chronic renal disease or prerenal azotaemia is present. Therefore, the status of renal function should be known before starting therapy in diabetic or suspected diabetic patients. Amizide should be discontinued for at least three days before glucose tolerance testing.

Insulin requirements in diabetic patients may be increased, decreased or unchanged due to the hydrochlorothiazide component. Latent diabetes mellitus may become manifest during thiazide administration.

*Metabolic or Respiratory Acidosis.* In severely ill patients in whom respiratory or metabolic acidosis may occur, antikaliuretic therapy should be instituted only with caution. Such patients include those with cardiopulmonary disease and those with decompensated 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.

*Hyperkalaemia.* Defined as serum potassium levels over 5.5 mmol/L, hyperkalaemia has been observed in patients who received amiloride hydrochloride either alone, or in combination with other diuretic drugs. This has been noted particularly in aged patients, diabetic 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.

Warning signs of hyperkalaemia include paraesthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and serum potassium and ECG abnormalities. As hyperkalaemia is not always associated with an abnormal electrocardiogram, careful monitoring of the plasma potassium level is important. When abnormal, the ECG in hyperkalaemia is characterised 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, and prolongation of the PR interval and ST depression.

In the event of hyperkalaemia occurring in patients taking Amizide, the drug should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level. Discontinuation of antikaliuretic

therapy should be followed by intravenous administration of sodium bicarbonate solution, or oral or parenteral glucose with a rapid-acting insulin. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given orally or by enema. Patients with persistent hyperkalaemia may require dialysis.

*Electrolyte Imbalance and Reversible 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: hyponatraemia, hypochloreaemic alkalosis, hypokalaemia and hypomagnesaemia. 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, confusion, restlessness, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hyponatraemia and hypochloreaemia may occur during the use of thiazide and other oral diuretics even when amiloride hydrochloride is used. Any chloride deficit during thiazide therapy is generally mild and may be lessened by the amiloride hydrochloride component of Amizide. Hypochloreaemia usually does not require specific treatment except under extraordinary circumstances (as in hepatic disease or renal disease). Dilutional hyponatraemia may occur in oedematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatraemia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalaemia 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 is usually prevented by the amiloride hydrochloride component of Amizide.

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

Reversible increases in BUN levels have been reported. These have accompanied vigorous fluid elimination, especially when diuretic combinations were used in seriously ill patients, such as those who have hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant oedema. Therefore, careful monitoring of serum electrolytes and BUN levels is important when Amizide is given to such patients.

*Azotaemia.* As azotaemia may be precipitated or increased by hydrochlorothiazide, special caution is necessary in patients with impaired renal function to avoid cumulative or toxic effects of the components. If increasing azotaemia and oliguria occur during treatment, Amizide should be discontinued.

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

Because calcium excretion is decreased by thiazides, Amizide should be discontinued before carrying out tests for parathyroid function. Pathological changes in the parathyroid glands, with hypercalcaemia and hypophosphataemia 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.

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

*Sensitivity Reactions.* Such reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

*Impaired Hepatic Function.* 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 with amiloride hydrochloride and hydrochlorothiazide.

## Use in Pregnancy (Category C)

Thiazides, amiloride, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy, products of this type should only be given on sound indications, and then in the lowest effective dose.

Because clinical experience is limited, Amizide is not recommended for use during pregnancy. Thiazides cross the placental barrier and appear in the cord blood. Therefore, the use of Amizide when pregnancy is present or suspected requires that the potential benefits of the drug must be weighed against possible hazards to the foetus. These hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other side effects that have occurred in the adult.

The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated.

*Australian categorisation definition of Category C.* Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

## Use in Lactation

Amizide is not recommended for use in breastfeeding mothers due to the fact that thiazides appear in breast milk. If use of the drug is considered to be essential, the patient should stop breastfeeding.

## Interactions with Other Medicines

### Medicines and foods that can interact with both hydrochlorothiazide and amiloride hydrochloride

*Alcohol.* Potentiation of orthostatic hypotension.

*Antihypertensive Drugs.* Additive effect and increased risk of first dose hypotension. To reduce the risk of first dose hypotension, diuretic therapy should be discontinued for 2 to 3 days and salt/volume depletion should be corrected prior to initiation of therapy with an ACE inhibitor, angiotensin receptor antagonist or alpha-adrenoceptor antagonist (alpha blocker).

*Amantadine.* Thiazide diuretics and amiloride may compete with amantadine for renal tubular secretion, leading to increased plasma concentrations of amantadine.

*Barbiturate or Narcotics.* Potentiation of orthostatic hypotension.

*Dofetilide.* Thiazide diuretics and amiloride compete with dofetilide for renal tubular secretion, leading to increased plasma concentrations of dofetilide. Hypokalemia and hypomagnesaemia caused by diuretics may also increase the risk of dofetilide toxicity.

*Drugs that prolong the QT interval (e.g. Astemizole Dofetilide, Droperidol, Pimozide, Sotalol, Terfenadine).* Diuretic-induced hypokalaemia and hypomagnesaemia increases the risk of arrhythmia with drugs that prolong the QT interval.

*Ephedrine, Pseudoephedrine.* Ephedrine and pseudoephedrine are present in various prescription medicines, over-the-counter cold and flu remedies and the complementary medicine Ma Huang (ephedra). These drugs may reduce the effectiveness of antihypertensive medications, including diuretics. Diuretic-induced hypokalaemia may increase the risk of premature ventricular contractions associated with ephedrine and pseudoephedrine.

*Liquorice.* Liquorice may reduce the antihypertensive effect of hydrochlorothiazide and amiloride. Liquorice may also increase the risk of diuretic-induced hypokalaemia.

*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 product information for lithium preparations before use.

*Nonsteroidal Anti-Inflammatory Drugs.* In some patients, the administration of a NSAID can reduce the diuretic, natriuretic and antihypertensive effects of diuretics. Concomitant administration of NSAIDs and potassium-sparing agents, including amiloride hydrochloride may cause hyperkalaemia and renal failure, particularly in elderly patients. Therefore, when amiloride hydrochloride is used concomitantly with NSAIDs, renal function and serum potassium level should be carefully monitored.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

*Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics.* The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

*Opioids.* Potentiation of orthostatic hypotension.

*Sulfonylureas (e.g. Chlorpropamide, Glibenclamide, Gliclazide, Glimepride, Tolbutamide).* Diuretics and sulfonylureas may have an additive hyponatraemic effect.

#### Other medicines that can interact with amiloride hydrochloride

*ACE Inhibitors, Angiotensin Receptor Antagonists.* Increased risk of hyperkalaemia.

*Cyclosporin.* Increased risk of hyperkalaemia.

*Indomethacin.* Increased risk of hyperkalaemia.

*Tacrolimus.* Increased risk of hyperkalaemia.

If concomitant use of the above agents and amiloride is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

*Quinidine.* The combination of amiloride and quinidine has been reported to have a proarrhythmic effect in patients with a history of ventricular tachycardia.

#### Other medicines that can interact with hydrochlorothiazide

*Allopurinol.* The risk of hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazides and allopurinol concurrently.

*Amphotericin B.* Increased risk of hypokalaemia.

*Antidiabetic Drugs (Oral Agents and Insulin).* Dosage adjustment of the antidiabetic drug may be required.

*Anti-neoplastic Drugs.* Thiazide diuretics may enhance the myelosuppressive effects of anti-neoplastic drugs.

*Beta-2 Agonists.* Increased risk of hypokalaemia.

*Calcium Salts, Calcitriol.* Increased risk of hypercalcaemia.

*Carbamazepine.* Increased risk of hyponatraemia.

*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 hypokalaemia.

*Diazoxide.* Potentiation of hyperuricemic and hypotensive effects. The combination of diazoxide and thiazide diuretics has also been reported to blunt insulin secretion and may cause hyperglycaemia.

*Pressor Amines (e.g. Noradrenaline).* Possible decreased response to pressor amines but not sufficient to preclude their use.

*Propranolol.* Increased risk of elevated blood glucose, triglycerides and uric acid.

*Nondepolarising Skeletal Muscle Relaxants (e.g. Tubocurarine).* Possible increased responsiveness to the muscle relaxant.

*Reboxetine.* Increased risk of hypokalaemia.

*Sulfamethoxazole, Trimethoprim.* An increased incidence of thrombocytopenia with purpura has been observed in elderly patients concurrently receiving sulfamethoxazole-trimethoprim and certain diuretics, primarily thiazides. Severe hyponatraemia has been reported in patients taking trimethoprim with hydrochlorothiazide or hydrochlorothiazide-amiloride.

*Tetracyclines.* The antianabolic action of tetracyclines may cause an increase in plasma urea levels. This effect may be enhanced by diuretics.

### Effects on Laboratory Tests

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

## ADVERSE EFFECTS

Amizide is usually well tolerated. Although minor adverse reactions have been reported relatively frequently, significant adverse effects have been reported infrequently.

Adverse effects that have been reported with Amizide 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.

### Amiloride/ Hydrochlorothiazide

*Cardiovascular.* Arrhythmia, tachycardia, digitalis toxicity, orthostatic hypotension, angina pectoris.

*Gastrointestinal.* Nausea, anorexia, vomiting, diarrhoea, constipation, abdominal pain, gastrointestinal bleeding, appetite changes, abdominal fullness, flatulence, thirst, hiccups.

*Metabolic.* Elevated serum potassium levels (> 5.5 mmol/L), electrolyte imbalance, hyponatraemia, gout, dehydration, symptomatic hyponatraemia.

<i>Dermatological.</i>	Rash, pruritus, flushing, diaphoresis.
<i>Musculoskeletal.</i>	Leg ache, muscle cramps, joint pain.
<i>Nervous System.</i>	Dizziness, vertigo, paraesthesia, stupor.
<i>Psychiatric.</i>	Insomnia, nervousness, mental confusion, depression, sleepiness.
<i>Respiratory.</i>	Dyspnoea.
<i>Special Senses.</i>	Bad taste, visual disturbance, nasal congestion.
<i>Genitourinary.</i>	Impotence, dysuria, nocturia, incontinence, renal dysfunction including renal failure.
<i>Body as a whole.</i>	Headache, weakness, fatigue, malaise, chest pain, back pain, syncope.

Other adverse effects that have been reported with the individual components are listed as follows:

#### Amiloride

<i>Gastrointestinal.</i>	Abnormal hepatic function, activation of probable pre-existing peptic ulcer, dyspepsia, jaundice.
<i>Dermatological.</i>	Dry mouth, alopecia, diaphoresis.
<i>Nervous System.</i>	Tremors, encephalopathy, numbness.
<i>Haematological.</i>	Aplastic anaemia, neutropenia.
<i>Cardiovascular.</i>	Peripheral ischaemia/gangrene (in combination with frusemide). One patient with partial heart block developed complete heart block; palpitations.
<i>Endocrine/Metabolic.</i>	Metabolic acidosis.
<i>Psychiatric.</i>	Decreased libido, somnolence.
<i>Respiratory.</i>	Cough.
<i>Special Senses.</i>	Tinnitus, increased intraocular pressure.
<i>Genitourinary.</i>	Polyuria, urinary frequency, bladder spasm.
<i>Body as a whole.</i>	Neck/shoulder ache, pain in extremities.

#### Hydrochlorothiazide

<i>Cardiovascular.</i>	Necrotising angiitis (vasculitis, cutaneous vasculitis), withdrawal oedema.
<i>Gastrointestinal.</i>	Jaundice (intrahepatic cholestatic jaundice), pancreatitis, cramping, gastric irritation, sialadenitis.
<i>Endocrine/ Metabolic.</i>	Glycosuria, hyperglycaemia, hyperuricaemia, hypokalaemia, zinc deficiency.
<i>Haematological.</i>	Agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, purpura, thrombocytopenia.
<i>Dermatological.</i>	Photosensitivity, urticaria, toxic epidermal necrolysis.
<i>Musculoskeletal.</i>	Myalgia.

<i>Psychiatric.</i>	Restlessness.
<i>Renal.</i>	Interstitial nephritis, urate calculi.
<i>Respiratory.</i>	Respiratory distress including pneumonitis and pulmonary oedema.
<i>Special Senses.</i>	Transient blurred vision, xanthopsia.
<i>Body as a whole.</i>	Anaphylactic reaction, fever.

## DOSAGE AND ADMINISTRATION

*Oedema of Cardiac Origin.* Initiate at a dosage of 1 or 2 tablets daily. Dosage may be increased if necessary, but must not exceed 4 tablets daily. 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.

*Hypertension.* The usual dosage is 1 or 2 tablets, given once a day or in divided doses. The dosage may be increased if necessary; but must not exceed 4 tablets per day.

*Hepatic Cirrhosis with Ascites* (see **Precautions**). Treatment should be initiated with a small dose (e.g. 1 tablet daily). If necessary, dosage may be increased gradually until there is effective diuresis. The dosage should not exceed 4 tablets daily. 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.

## OVERDOSAGE

No data are available with regard to overdosage in humans. The oral LD<sub>50</sub> 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 dialysable.

No specific information is available on the treatment of overdosage with Amizide and no specific antidote is available. Treatment is symptomatic and supportive. Therapy with Amizide should be discontinued and the patient observed closely. Activated charcoal may reduce absorption of hydrochlorothiazide and amiloride if given within one or two hours after ingestion. In patients who are not fully conscious or who have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

*Amiloride hydrochloride.* 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 rats and mice.

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

## PRESENTATION AND STORAGE CONDITIONS

**Amizide**, hydrochlorothiazide 50 mg with amiloride hydrochloride 5 mg tablet: off-white, marked H breakline A on one side,  $\alpha$  on reverse; bottles of 30 and 50 tablets.

Store below 30°C.

## NAME AND ADDRESS OF THE SPONSOR

**Alphapharm Pty Limited**

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## POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

20/09/1991

## DATE OF MOST RECENT AMENDMENT

20/05/2013