PLEASE READ CAREFFULLY

Amilozide Tablet

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Each tablet contains amiloride hydrochloride 5.0 mg and hydrochlorothiazide 50.0 mg.

DESCRIPTION

Orange rhombus biconvex tablet.

INDICATIONS

Amilozide Tablet is initiated in patients whom potassium depletion might be suspected or anticipated. **Amilozide Tablet**, the combination of amiloride hydrochloride and hydrochlorothiazide, minimizes the possibility of excessive potassium loss in patients during vigorous diuresis for prolonged periods. **Amilozide Tablet** with the potassium sparing component of amiloride hydrochloride is specially indicated for those conditions, where the positive effect of potassium balance in patient is particularly important.

Amilozide Tablet may be used alone or as an adjunctive to other antihypertensive drugs. Since amiloride hydrochloride and hydrochlorothiazide enhances the action of these antihypertensive agents, dosage adjustment may be necessary to avoid excessive fall in blood pressure and any other untoward side effects.

Amilozide Tablet is indicated in the treatment of:

- Hypertension.
- Oedema of cardiac origin.
- Hepatic cirrhosis with ascites.

RECOMMENDED DOSAGE

Hypertension

The usual dose is 1 or 2 tablets of **Amilozide Tablet** daily or in divided doses. The dosage may be increased if necessary but must not exceed 4 tablets a day.

Oedema of Cardiac Origin

Amilozide Tablet may be started at a dosage of 1 or 2 tablets daily. 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.

Hepatic Cirrhosis with Ascites

Treatment should be initiated with 1 tablet of **Amilozide Tablet** daily. If necessary, dosage may be increased gradually until effective diuresis is achieved. The dosage should not exceed 4 tablets a day.

Maintenance doses may be lower than those required to initiate diuresis. Therefore, reduction in daily dose should be attempted once the patient's weight has stabilized. Gradual weight reduction in cirrhotic patients is especially desirable to reduce the likelihood of unwanted reactions associated with diuretic therapy.

Dosage adjustment may be required for elderly people. Renal function and clinical response should be taken into account when dosage adjustment is carried out.

Mode of administration: Oral

CONTRAINDICATIONS

- Hypersensitivity to amiloride hydrochloride, hydrochlorothiazide, any of the excipients listed or other sulphonamide derived drugs.
- Hyperkalaemia (plasma potassium over 5.5 mmol/l); other potassium-conserving diuretics. Potassium supplements or potassium rich foods (except in severe and/or refractory cases of hypokalaemia under careful monitoring).
- Hypercalcaemia.
- Severe renal impairment; severe progressive renal disease; acute renal failure; anuria; use of potassium conserving agents may result in rapid development of hyperkalaemia in patients with renal impairment; patients with blood urea over 10 mmol/L or those with serum creatinine over 130 µmol/L in whom serum electrolyte and blood urea levels cannot be monitored carefully and frequently.
- Severe hepatic failure; precoma associated with hepatic cirrhosis.
- Diabetic nephropathy; patients with diabetes mellitus.
- Addison's disease.
- Concomitant treatment with spironolactone or triamterene.
- Concurrent lithium therapy.
- The safety of amiloride hydrochloride for use in children under 18 years of age has not been established. **Amilozide Tablet** is not recommended for children. For use in pregnancy and use in breastfeeding mothers, see section *Pregnancy and Lactation*.

WARNINGS AND PRECAUTIONS

Hyperkalaemia

Hyperkalaemia has been observed in patients receiving amiloride hydrochloride, either alone or with other diuretics, particularly in the aged and in diabetics. Hyperkalaemia has been reported in seriously ill hospital patients with congestive heart failure or hepatic cirrhosis who had renal impairment, or were undergoing vigorous diuretic therapy.

Such patients should be carefully observed for laboratory, clinical and ECG evidence of hyperkalaemia (which may not always be associated with an abnormal ECG). Some deaths have been reported in this group of patients.

Treatment of hyperkalaemia

Should hyperkalaemia develop, **Amilozide Tablet** should be discontinued immediately. If necessary, active measures should be taken to reduce the serum potassium to normal.

Impaired renal function

Due to the risk of developing hyperkalaemia, patients with impaired renal function should be monitored carefully for serum electrolytes and blood urea levels, as should seriously ill patients, such as those with hepatic cirrhosis with ascites and metabolic alkalosis or those with resistant oedema who are also taking diuretics. Thiazide diuretics become ineffective when creatinine clearance falls below 30ml/min.

Electrolyte imbalance and blood urea increases

Although the likelihood of electrolyte imbalance is reduced by **Amilozide Tablet**, careful check should be kept for such signs of fluid and electrolyte imbalance hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia. [Particularly in the elderly and in patients receiving long-term therapy and in the presence of excessive vomiting or during parenteral fluid therapy.]

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

Hypokalaemia may develop, especially as a result of brisk diuresis, after prolonged therapy or when severe cirrhosis is present. A potassium chloride supplement is recommended in these circumstances, however, neither potassium supplements nor a potassium-rich diet should be used with **Amilozide Tablet** except under careful monitoring in severe and/or refractory cases of hypokalaemia. Potassium conserving therapy should be initiated with caution in severely ill patients in whom metabolic or respiratory acidosis may occur, e.g., patients with decompensated diabetes or cardiopulmonary disease. Shifts in acid base balance alter the balance of extracellular/intracellular potassium. The development of acidosis may be associated with rapid increases in serum potassium. Potassium replacement or conservation is also likely to be necessary in patients at risk from the cardiac effects of hypokalaemia such as those with severe heart disease, those taking cardiac glycosides preparations or high doses of diuretics and in patients with severe liver disease. Potassium supplements should not be given in renal insufficiency complicated by hyperkalaemia. Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium. Magnesium depletion has also been implicated as a risk factor for arrhythmias.

Some patients may be particularly susceptible to hyponatraemia, including the elderly and those with severe heart failure who are very oedematous, particularly with large doses of thiazides in conjunction with restricted salt in the diet. Diuretic-induced hyponatraemia is usually mild and asymptomatic. It may become severe and symptomatic in a few patients who will then 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. Therapy should be discontinued before carrying out test for parathyroid function.

In seriously ill patients, reversible increases in blood urea have been reported accompanying vigorous diuresis, hepatic cirrhosis, ascites and metabolic alkalosis or those with resistant oedema. Serum electrolyte and blood urea levels should be carefully monitored in these patients. **Amilozide Tablet** should be used with caution in patients with renal impairment. Special care should be taken to avoid cumulative or toxic effects due to a reduced excretion of its components (see section *Contraindications*). Uraemia may be precipitated or increased by hydrochlorothiazide. **Amilozide Tablet** should be discontinued if increasing oliguria and uraemia occurs during treatment.

Liver disease

Use with caution in hepatic impairment or progressive liver disease. As a result of associated aldosteronism, oral diuretic therapy is more frequently accompanied by adverse reactions in patients with hepatic cirrhosis and ascites because these patients are intolerant of acute shifts in electrolyte balance (which may precipitate hepatic coma) and because they often have pre-existing hypokalaemia. Use in severe hepatic failure is contraindicated.

Metabolic

Hyperuricaemia may occur or gout may be precipitated or aggravated in certain patients receiving thiazides.

Thiazides may impair glucose tolerance. Diabetes mellitus may be precipitated or aggravated by therapy with **Amilozide Tablet**. Dosage adjustment of antidiabetic agent, including insulin, may be required.

Amilozide Tablet should be discontinued at least three days before glucose tolerance tests are performed in patients with diabetes or suspected diabetes mellitus, especially if there is renal insufficiency or diabetic nephropathy, because of the risks of provoking severe hyperkalaemia.

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

Other

Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma. Caution is required in patients with severe asthma, as hypokalaemia associated with beta-2-agonist therapy can be potentiated by concurrent use of diuretics.

It has been reported that the thiazides may possibly activate or exacerbate systemic lupus erythematosus.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulphonamide or sulphonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible.

Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, **Amilozide Tablet** should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

DRUG INTERACTIONS

- Alcohol: Co-administration of alcohol may potentiate orthostatic hypotension.
- Aldesleukin: Enhanced hypotensive effect.
- Anaesthetics, general: Enhanced hypotensive effect.
- Analgesics: Some non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), may attenuate the effect of antihypertensive drugs, including the diuretic, natriuretic and antihypertensive effects of diuretics.
- NSAIDs increase the risk of hyperkalaemia with potassium-sparing diuretics, including amiloride, particularly in elderly patients. When amiloride is used concomitantly with NSAIDs, serum potassium levels should be carefully monitored.
- Diuretics may increase the risk of nephrotoxicity of NSAIDs. 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 NSAIDs, including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or angiotensin-converting enzyme inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The combination should be administered with caution in patients with compromised renal function.
- Anion-exchange resins: Cholestyramine and colestipol reduce absorption of thiazides. 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%, respectively. When cholestyramine is given 4 hours after the hydrochlorothiazide, the absorption of hydrochlorothiazide is reduced by 30 to 35%.
- Antiarrhythmics: Toxicity of amiodarone, disopyramide, flecainide and quinidine are increased if hypokalaemia occurs. Action of lidocaine and mexiletine is antagonised by hypokalaemia. Hypokalaemia increases risk of ventricular arrhythmias with sotalol, a beta-blocker. The antiarrhythmic activity of quinidine may be opposed by amiloride.
- Antibacterials: Severe hyponatraemia may occur with concomitant administration of hydrochlorothiazide and trimethoprim.
- Antidepressants: Co-administration of tricyclic antidepressants may potentiate orthostatic hypotension. Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs). Possibly increased risk of hypokalaemia if thiazides given with reboxetine.
- Antidiabetics: Thiazides may antagonise the hypoglycaemic effect of antidiabetics. Oral and parenteral antidiabetic drugs may require adjustment of dosage with concurrent use. **Amilozide Tablet** can act synergistically with chlorpropamide to increase the risk of hyponatraemia.
- Antiepileptic: Although rare, increased risk of hyponatraemia with concomitant use of carbamazepine and thiazide diuretics such as bendroflumethiazide.
- Antifungals: Increased risk of hypokalaemia with concurrent use of thiazide diuretics and amphotericin. Hydrochlorothiazide may increase the plasma concentration of fluconazole.
- Antigout agents: Potential for increased toxicity and hypersensitivity/allergic reactions with concomitant use of allopurinol and thiazide diuretics.
- Antihistamines: Hydrochlorothiazide-induced hypokalaemia may increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole and terfenadine.
- Antihypertensive: Diuretics may enhance the hypotensive action of other hypotension producing medications, including angiotensin-converting enzyme (ACE) inhibitors (enhanced first-dose hypotension), angiotensin-II antagonists, calcium channel blockers, beta-blockers, alpha-blockers (increased risk of first-dose hypotension with alpha blockers such as prazosin), hydralazine or diazoxide. The dosage of concurrently administered antihypertensive drugs, especially adrenergic-blockers, may need to be reduced when **Amilozide Tablet** is added to the regimen. Enhanced hypotensive effect, risk of severe hyperkalaemia with potassium-sparing diuretics. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium. Diuretic therapy should be discontinued for two to three days prior to initiation of therapy with an ACE inhibitor to reduce the likelihood of first dose hypotension. Concurrent administration of thiazides with beta-blockers or diazoxide has the potential to produce hyperglycaemia which may necessitate adjustment of the dose of antidiabetic medication including insulin. There have been reports of intravascular immune haemolysis in patients taking hydrochlorothiazide and methyldopa.
- Antimalarials: Hydrochlorothiazide-induced hypokalaemia may increase the risk of arrhythmias with drugs that prolong the QT interval, such as halofantrine.
- Antipsychotics: Diuretic-induced hypokalaemia increases the risk of ventricular arrhythmias with pimozide and sertindole, concurrent use should be avoided. Enhanced hypotensive effect with phenothiazines.
- Barbiturates: Co-administration of barbiturates may potentiate orthostatic hypotension.
- Calcium salts & vitamins: There is a risk of hypercalcaemia with calcium salts and vitamin D. There is an increased risk of developing milk-alkali syndrome in patients given large amounts of calcium or vitamin D in combination with thiazides.
- Cardiac glycosides: Increased risk of toxicity if diuretic- induced hypokalaemia occurs. Diuretic-induced hypokalaemia intensifies the effect of cardiac glycosides on cardiac muscle and treatment with cardiac glycosides may have to be temporarily suspended.
- Corticosteroids or ACTH: Increased risk of thiazide-induced electrolyte depletion, particularly hypokalaemia, mainly with the naturally occurring corticosteroids such as cortisone and hydrocortisone. The synthetic corticosteroids have a much less marked potassium-losing effect. Fluid retention associated with corticosteroid use may antagonise the diuretic/antihypertensive effect.
- Diuretics: Increased risk of hypokalaemia with concurrent administration of other thiazides and other diuretics including

acetazolamide and loop diuretics.

- Dopaminergics: Potential for increased risk of amantadine toxicity in association with hydrochlorothiazide. Enhanced hypotensive effect with levodopa.
- Hormones and other endocrine drugs: Combined oral contraceptives and oestrogens may antagonise the diuretic effect. There is a risk of hyperkalaemia with trilostane. Thiazide diuretics may increase the risk of hypercalcaemia with toremifene. Oestrogen antagonises diuretic effect.
- Immunosuppressants: When amiloride hydrochloride is administered concomitantly with ciclosporin or tacrolimus, the risk of hyperkalaemia may be increased. If concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium. Increased risk of nephrotoxicity and/or hypermagnesaemia with concomitant use of ciclosporin and thiazide diuretics.
- Lithium: Lithium may accumulate as a result of reduced renal clearance; increased risk of lithium toxicity. Lithium generally should not be given with diuretics. Refer to the prescribing information for lithium preparations before use of such preparations.
- Muscle relaxants: Enhanced hypotensive effect may occur with tizanidine. Diuretic-induced hypokalaemia may potentiate the blockade of non-depolarising neuromuscular blocking agents such as tubocurarine, increasing muscle relaxation.
- Nitrates: Enhanced hypotensive effect.
- Potassium conserving agents: When amiloride is administered concomitantly with potassium conserving agents or potassium supplements, there is an increased risk of hyperkalaemia (see section *Contraindications*).
- Prostaglandins: Hypotensive effect may be potentiated by alprostadil.
- Sympathomimetics: Increased risk of hypokalaemia with thiazide diuretics and high doses of beta-2 sympathomimetics (see section *Warnings and Precautions,* use of beta-2-agonists in severe asthma). Pressor amines such as adrenaline may show decreased arterial responsiveness when used with **Amilozide Tablet** but this reaction is not enough to preclude their therapeutic usefulness.
- Ulcer-healing drugs: Fluid retention associated with carbenoxolone may cause antagonism of diuretic/antihypertensive effect. Thiazides can be used to treat the adverse side-effects of carbenoxolone, but not amiloride which may antagonise the ulcer-healing effect.
- Vitamins: see under Calcium salts & vitamins.
- Drug/laboratory tests: Because thiazides may affect calcium metabolism, **Amilozide Tablet** may interfere with tests for parathyroid function. Hydrochlorothiazide should be stopped before parathyroid function is tested.
- Creatinine clearance: Amiloride can block the tubular secretion of creatinine and may lead to falsely high measurements of creatinine clearance.

PREGNANCY AND LACTATION

Pregnancy

Diuretics

The routine use of diuretics in otherwise healthy pregnant women with or without oedema is not indicated, because they may be associated with hypovolaemia, increased blood viscosity and decreased placental perfusion. Diuretics do not prevent the development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful for its treatment.

Hydrochlorothiazide

There is limited experience hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance, bone marrow depression and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation

Although it is not known whether amiloride hydrochloride is excreted in human milk, it is known that hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of **Amilozide Tablet** during breast feeding is not recommended. If **Amilozide Tablet** is used during breast feeding, doses should be kept as low as possible.

SIDE EFFECTS

Although minor side effects are relatively common, significant side effects are infrequent. Reported side effects are generally associated with diuresis, thiazide therapy or with the underlying disease. No increase in the risk of adverse reactions has been seen over those of the individual components.

The following side effects have been reported with **Amilozide Tablet**, and additional side effects of amiloride and hydrochlorothiazide alone:

System organ class	**Preferred term**
Immune system disorders	Anaphylactic reaction.
Metabolism and nutrition disorders	Appetite changes, anorexia, gout, dehydration.
Electrolyte balance	Elevated plasma potassium levels (above 5.5mmol/l) electrolyte imbalance, hyponatraemia, (see section *Warnings and Precautions*) and symptomatic hyponatraemia. Hyponatraemia as a complication is rare, but constitutes a medical emergency as onset may be rapid. The symptoms of hyponatraemia may be non-specific and include nausea, lethargy, weakness, irritability, mental confusion, muscle cramps and anorexia, but it may be an important cause of morbidity. Severe sequelae of hyponatraemia include tonic-clonic seizure and clinical features resembling subarachnoid haemorrhage.

Psychiatric disorders	Insomnia, nervousness, mental confusion, depression.
Nervous system disorders	Headache, dizziness, sleepiness, syncope, paraesthesia and stupor, bad taste.
Eye disorders	Visual disturbances.
Ear disorders	Vertigo.
Cardiac disorders	Arrhythmias, tachycardia, angina pectoris.
Vascular disorders	Orthostatic hypotension, flushing.
Respiratory, thoracic and mediastinal disorders	Dyspnoea, hiccups, nasal congestion.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, constipation, abdominal pain, gastrointestinal bleeding, abdominal fullness, flatulence.
Skin and subcutaneous tissue disorders	Rash, pruritus, diaphoresis.
Musculoskeletal and connective tissue disorders	Leg ache, muscle cramps, joint pain, back pain.
Renal and urinary disorders	Nocturia, renal dysfunction including renal failure, dysuria, incontinence.
Reproductive system and breast disorders	Impotence occurring early during treatment (onset after 2 years unlikely) and reversible on withdrawal of treatment.
General disorders and administration site conditions	Chest pain, fatigue, malaise, weakness and thirst.
Injury, poisoning and procedural complication	Digitalis toxicity (see section *Drug Interactions*, subheading Cardiac Glycosides).
Amiloride	
Blood and lymphatic system disorders	Aplastic anaemia and neutropenia.
Metabolism and nutrition disorders	Hyperkalaemia (see also section *Contraindication* and *Warnings and Precautions*).
Psychiatric disorders	Decreased libido.
Nervous system disorders	Somnolence encephalopathy, tremors.
Ear disorders	Tinnitus.
Cardiac disorders	One patient with partial heart block developed complete heart block. Palpitations.
Respiratory, thoracic and mediastinal disorders	Cough.
Gastrointestinal disorders	Activation of probable pre-existing peptic ulcer, dyspepsia, dry mouth.
Hepatobiliary disorders	Abnormal liver function. A deepening of jaundice has occurred in cirrhotic patients receiving amiloride hydrochloride alone, but the relationship to amiloride is uncertain.
Skin and subcutaneous tissue disorders	Alopecia.
Musculoskeletal and connective tissue disorders	Neck/shoulder ache, pain in extremities.
Renal and urinary disorders	Polyuria, urinary frequency, bladder spasm
Investigations	Increased intra-ocular pressure.
Hydrochlorothiazide	
Infections and infestations	Sialadenitis.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency 'not known': non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).
Blood and lymphatic system disorders	Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
Immune system disorders	Hypersensitivity reactions.
Metabolism and nutrition disorders	Hyperglycaemia glycosuria, diabetes mellitus may be aggravated and latent diabetes may become manifest during thiazide administration. Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change (see section *Drug Interactions*). Hypokalaemia, hypochloraemic alkalosis, the urinary excretion of calcium may be reduced and the potential for hypercalcaemia exists (use in pre-existing hypercalcaemia is contraindicated). Hyperuricaemia may occur or gout may be precipitated or aggravated in patients receiving thiazides.
Psychiatric disorders	Restlessness.
Nervous system disorders	Encephalopathy may be precipitated by hypokalaemia in patients with pre-existing liver disease.

Eye disorders	Transient blurred vision and xanthopsia Frequency 'not known': Choroidal effusion, acute myopia, acute angle-closure glaucoma.
Vascular disorders	Necrotising angiitis, vasculitis.
Respiratory, thoracic and mediastinal disorders	Respiratory distress including pneumonitis, pulmonary oedema. Frequency 'very rare': acute respiratory distress syndrome (ARDS).
Gastrointestinal disorders	Cramping, gastric irritation and pancreatitis.
Hepatobiliary disorders	Jaundice (intrahepatic cholestatic jaundice).
Skin and subcutaneous tissue disorders	Urticaria, photosensitivity, which may persist after thiazide withdrawal. Cutaneous vasculitis. Purpura. Toxic epidermal necrolysis.
Renal and urinary disorders	Interstitial nephritis, glycosuria.
General disorders and administration site conditions	Fever.
Description of selected adverse reactions	Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

SYMPTOMS & TREATMENT OF OVERDOSAGE

Symptoms of overdose:

The most likely signs and symptoms of overdosage with amiloride are those attributable to fluid depletion (dehydration, hypotension) and electrolyte imbalance.

Electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration are the most common signs and symptoms of hydrochlorothiazide overdosage. If cardiac glycosides have been administered, hypokalaemia may accentuate cardiac arrhythmias.

Treatment of overdose:

No specific data are available on overdose with **Amilozide tablet**. No specific antidote is available and it is not known whether the drug is dialyzable. Treatment should be symptomatic and supportive. Therapy should be discontinued and the patient watched closely. Patients who present within one hour of an overdose may be administered activated charcoal. Symptomatic treatment should include monitoring serum electrolyte concentrations, renal function and fluid and electrolyte replacement. Blood pressure should be monitored and corrected when necessary. If hyperkalaemia occurs, active measures should be taken to reduce the plasma potassium levels.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Side effects such as headache, visual disturbances, dizziness, weakness, fatigue, stupor and vertigo may occur. Should these occur, the patient should be cautioned not to drive or operate any machinery.

PHARMACODYNAMICS

Amiloride

A mild diuretic acting on distal renal tubules, increasing excretion of sodium and chloride and reducing potassium excretion.

Hydrochlorothiazide

A diuretic that acts by reducing reabsorption of electrolytes from renal tubules, thereby increasing the excretion of sodium and chloride ions and consequently of water. Potassium ions are excreted to a lesser extent. Hydrochlorothiazide also has a blood pressure lowering effect and enhances the effects of other antihypertensive agents.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose-response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000mg).

PHARMACOKINETICS

Amiloride

Acts in 2 hours, completely absorbed from intestinal tract. Biological half-life 6 hours, excreted unchanged partly in urine. Peak serum levels reached in 4 hours.

Hydrochlorothiazide

The plasma half-life of hydrochlorothiazide is 5.6 hours with a subsequent longer terminal half-life. Peak plasma concentration reached in 1.5 to 3 hours, with diuresis lasting for 12 hours.

Excipients: Lactose monohydrate, corn starch, pregelatinize starch, sodium starch glycolate, talc, magnesium stearate, polysorbate 80, sunset yellow.

STORAGE CONDITIONS

Do not store above 30°C. Protect from light.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

PACKING/PACK SIZES

Clear brown PVC blister strip of 10 tablets per strip. Available in box of 10 and 50 strips.

MANUFACTURED BY

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