SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amilozide 2.5mg/25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Amiloride hydrochloride 2.5mg and hydrochlorothiazide 25mg

Excipient with known effect: Each tablet contains 40mg lactose (as lactose anhydrous)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
A slightly yellow, round, scored tablets with bevelled edge, with an approximate diameter of 7mm with the code EZ/3 on one side

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-amilozide is indicated in patients with: hypertension, congestive heart failure, or hepatic cirrhosis with ascites and oedema. In hypertension, Co-amilozide may be used alone or in conjunction with other antihypertensive agents.

Co-amilozide is intended for the treatment of patients in whom potassium depletion might be suspected or anticipated.

The presence of amiloride hydrochloride minimises the likelihood of potassium loss during vigorous diuresis for long-term maintenance therapy. The combination is thus indicated especially in conditions where potassium

balance is particularly important e.g. patients with congestive heart failure receiving digitalis.

4.2 Posology and method of administration

Posology

The rate of loss of weight and the serum electrolyte levels should determine the dosage. The most satisfactory rate of weight loss after initiation of diuresis is about 0.5-1.0 kg/day.

Hypertension

Initially one Co-amilozide 2.5mg/25mg tablet given once a day. If necessary, an increase to two Co-amilozide 2.5mg/25mg tablets given once a day or in divided doses.

Co-amilozide may be used alone or as an adjunct to other antihypertensive drugs, but since the antihypertensive effect of these agents may be enhanced, their dosage may need to be reduced in order to reduce the risk of an excessive drop in pressure.

Congestive heart failure

Initially one Co-amilozide 2.5mg/25mg tablet a day, subsequently adjusted if required, but not exceeding four Co-amilozide 2.5mg/25mg tablets a day. Optimal dosage is determined by the diuretic response and the plasma potassium level. Once an initial diuresis has been achieved, reduction in dosage may be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

Patients with hepatic cirrhosis with ascites

Initiate therapy with a low dose. A single daily dose of two Co-amilozide 2.5mg/25mg tablets may be increased gradually until there is an effective diuresis. Dosage should not exceed four Co-amilozide 2.5mg/25mg tablets a day. Maintenance dosages may be lower than those required to initiate diuresis; dosage reduction should therefore be attempted when the patient's weight is stabilised. A gradual weight reduction is especially desirable in cirrhotic patients to reduce the likelihood of untoward reactions associated with diuretic therapy.

Paediatric population:

Co-amilozide 2.5mg/25mg Tablets are not recommended for children under 18 years of age because safety and efficacy have not been established (see section 4.3).

Elderly patients

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance; the dosage should be carefully adjusted to renal function and clinical response. (See also Special Warnings & Precautions, subsections - Hyperkalaemia, Electrolyte imbalance).

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substances: amiloride hydrochloride, hydrochlorothiazide, other sulfonamide-derived drugs or to any of the excipients listed in section 6.1;
- Hyperkalaemia (plasma potassium over 5.5 mmol/1); other potassium-conserving diuretics. Potassium supplements or potassium-rich food (except in severe and/or refractory cases of hypokalaemia under careful monitoring);
- Concomitant use with spironolactone or triamterene;
- Severe hepatic failure, precoma associated with hepatic cirrhosis:
- Addison's disease;
- Hypercalcaemia;
- Concurrent lithium therapy;
- Diabetic nephropathy, patients with blood urea over 10 mmol/l, patients with diabetes mellitus;
- 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 over10 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;
- The safety of amiloride hydrochloride for use in children under 18 years of age has not been established. Co-amilozide is not recommended for children. For “use in pregnancy” and “use in breast-feeding mothers”, see section 4.6 (Pregnancy and lactation).

4.4 Special warnings and precautions for use

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

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

Treatment of hyperkalaemia: Should hyperkalaemia develop, discontinue Co-amilozide treatment immediately and, if necessary, take active measures taken to reduce the serum potassium to normal.

Impaired renal function: 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 because the use of Co-amilozide in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine clearance falls below 30 ml/min.

Electrolyte imbalance and blood urea increases: Although the likelihood of electrolyte imbalance is reduced with Co-amilozide, careful check should be kept for such signs of fluid and electrolyte imbalance as hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia, particularly in the elderly and in patients receiving long-term therapy. 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 or electrolyte imbalance include: dryness of the mouth, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea and vomiting (see also 4.8 Undesirable Effects, Electrolyte Imbalance).

Hypokalaemia may develop, especially as a result of brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability). A potassium chloride supplement is recommended in these circumstances, however, neither potassium supplements nor a potassium-rich diet should be used with co-amilozide 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, eg 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 tests 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. Co-amilozide 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 4.3 Contraindications).

Uraemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing uraemia and oliguria develop during treatment, Co-amilozide should be discontinued.

Hepatic disease: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease (see 4.3 'Contraindications'), since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. 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 (see 4.8 Undesirable Effects).

Metabolic: Hyperuricaemia may occur, or gout may be precipitated or aggravated in certain patients receiving thiazides (see 4.8 Undesirable Effects, Metabolic subsection).

Thiazides may impair glucose tolerance. Diabetes mellitus may be precipitated or aggravated by therapy with Co-amilozide (see 4.3 'Contraindications'). 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 determined before initiating therapy with Co-amilozide. Therapy should be discontinued at least three days before giving a glucose tolerance test. Potassium-conserving therapy should be initiated only with caution in severely ill patients in whom metabolic or respiratory acidosis may occur, e.g., patients with cardiopulmonary disease or 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 plasma potassium.

Sensitivity reactions: The possibility that thiazides may activate or exacerbate systemic lupus erythematosus has been reported.

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.

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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 minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
Sulfonamide or sulfonamide 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 visual 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 sulfonamide or penicillin allergy.

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, Co-amilozide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Wheat Starch
This medicine contains only very low levels of gluten (from wheat starch) and is very unlikely to cause problems in patients with coeliac disease. Patients with wheat allergy should not take this medicine. One Co-amilozide 2.5/25mg tablet contains no more than 4.15 micrograms gluten.

4.5 Interaction with other medicinal products and other forms of interaction

Aldesleukin: Enhanced hypotensive effect.

Anaesthetics, general: Enhanced hypotensive effect.

Lithium generally should not be given with diuretics (see 4.3 Contraindications). Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the prescribing information for lithium preparations before use of such preparations.

Analgesics: Some Non-Steroidal Anti-inflammatory Agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), may reduce the effect of antihypertensive drugs, including the diuretic, natriuretic and antihypertensive effects of diuretics.

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 ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Concomitant administration of NSAIDs and potassium-sparing agents, including amiloride, may cause hyperkalaemia, particularly in elderly patients. Therefore, when amiloride is used concomitantly with NSAIDs, serum potassium levels should be carefully monitored. When amiloride is administered concomitantly with ACE inhibitors, angiotensin II receptor antagonists, trilostane, ciclosporin or tacrolimus, the risk of hyperkalaemia may be increased.

Alcohol or barbiturates: Co-administration may potentiate orthostatic hypotension.

Anti-arrhythmics: Toxicity of amiodarone, disopyramide, flecainide and quinidine is increased if hypokalaemia occurs. Action of lidocaine and mexilitine 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. Co-amilozide can act synergistically with chlorpropamide to increase the risk of hyponatraemia.

Antiepileptics: Although rare, increased risk of hyponatraemia with concomitant use of carbamazepine and thiazide diuretics such as bendroflumethizide.

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.

Antihypertensives: 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 co-amilozide 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.

Other antihypertensive drugs may have an additive effect. Therefore, the dosage of these agents, especially adrenergic-blockers, may need to be reduced when Co-amilozide is added to the regimen. 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. 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 primozide and sertindole, concurrent use should be avoided. Enhanced hypotensive effect with phenothiazines.

Calcium salts and 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.

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 gastro-intestinal 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%.

Corticosteroids or ACTH may intensify any 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. Oestrogens antagonise 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.

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

Prostaglandins: Hypotensive effect may be potentiated by alprostadil.

Sympathomimetics: increased risk of hypokalaemia with thiazide diuretics and high doses of $beta_2$ sympathomimetics (See 4.4 Warnings and Precautions, use of beta 2 -agonists in severe asthma).

Pressor amines such as epinephrine (adrenaline) may show decreased arterial responsiveness when used with Co-amilozide 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.

Drug/laboratory tests: Because thiazides may affect calcium metabolism, Co-amilozide 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Diuretics

The routine use of diuretics in otherwise healthy pregnant women with or without mild 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 with 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.

Breast-feeding
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 Co-amilozide during breast-feeding is not recommended. If Co-amilozide is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable 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 Co-amilozide and additional side-effects of amiloride and hydrochlorothiazide alone:

Immune system disorders: anaphylactic reaction.

Metabolism and nutrition disorders: anorexia, gout, appetite changes, dehydration.

Electrolyte Balance: elevated plasma potassium levels (above 5.5 mmol/l), electrolyte imbalance, hyponatraemia (see 4.4 'Special warnings and precautions for use') 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 seizures and clinical features resembling subarachnoid haemorrhage.

Nervous system disorders: headache, dizziness, sleepiness, syncope, paraesthesia, stupor, poor taste.

Psychiatric disorders: insomnia, nervousness, mental confusion, depression.

Respiratory: dyspnoea.

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 in the course of 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 complications: digitalis toxicity (see 4.5 Interactions, sub-heading Cardiac Glycosides).

Amiloride:

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.

Blood and lymphatic system disorders: aplastic anaemia, neutropenia.

Metabolism and nutrition disorders: hyperkalaemia (see also 4.3 Contraindications and 4.4 Special Warnings & Precautions).

Cardiac disorders: one patient with partial heart block developed complete heart block, palpitations.

Psychiatric disorders: decreased libido.

Nervous system disorders: somnolence., encephalopathy, tremors

Respiratory, thoracic and mediastinal disorders: cough.

Ear disorders: tinnitus.

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.

General disorders and administration site conditions: fever.

Vascular disorders: necrotising angiitis, vasculitis.

Gastrointestinal disorders: pancreatitis, cramping, gastric irritation.

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 4.5 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, see 4.3). Hyperuricaemia may occur or gout may be precipitated or aggravated in patients receiving thiazides.

Nervous system disorders: encephalopathy may be precipitated by hypokalaemia in patients with pre-existing liver disease.

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.

Blood and lymphatic system disorders: agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, thrombocytopenia.

Psychiatric disorders: restlessness.

Immune system disorders: hypersensitivity reactions.

Renal and urinary disorders: interstitial nephritis, glycosuria.

Respiratory, thoracic and mediastinal disorders: respiratory distress, including pneumonitis, pulmonary oedema.
Very rare: Acute Respiratory Distress Syndrome (ARDS) (see section 4.4).

Eye disorders: transient blurred vision, xanthopsia, choroidal effusion.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Frequency not known: non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Description of selected adverse reactions: non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Treatment of overdose:
No specific data are available on overdosage with Co-amilozide.

No specific antidote is available and it is not known whether the drug is dialysable.

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 where necessary. If hyperkalaemia occurs, active measures should be taken to reduce the plasma potassium levels.

Symptoms of overdose:
The most common signs and symptoms of overdosage with amiloride hydrochloride are those attributable to fluid depletion (dehydration, hypotension) and electrolyte imbalance. Blood pressure should be monitored and corrected when necessary. If hyperkalaemia occurs, active measures should be taken to reduce the serum potassium levels.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretic and potassium-sparing agent
ATC code: C03EA01

Mechanism of action
Hydrochlorothiazide is a diuretic with antihypertensive properties. It acts by inhibiting the renal tubular reabsorption of sodium and chloride ions, which are excreted with an accompanying volume of water. Potassium excretion is also promoted.

Amiloride hydrochloride is a potassium-sparing diuretic. It also promotes the excretion of sodium and chloride, but it reduces the excretion of potassium.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide 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 hydrochlorothiazide: 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 (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Hydrochlorothiazide

About 70% of an oral dose of hydrochlorothiazide is absorbed. It has a plasma half-life of 5.6 to 14.8 hours with a subsequent longer terminal half-life.

Peak plasma concentration reached in 1.5 to 3 hours, with diuresis lasting for 12 hours.

It is excreted unchanged in the urine. It crosses the placental barrier and is secreted in breast milk.

Amiloride

About 50% of an oral dose of amiloride hydrochloride is absorbed. It has a plasma half-life of about 6 to 9 hours, but its effects may persist for up to 48 hours after a single dose.

It is excreted unchanged in the urine and faeces.

Peak serum levels reached in 4 hours.

5.3 Preclinical safety data

Amiloride and hydrochlorothiazide have been used in clinical practice for over 20 years and have become commonly used in combination.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Wheat starch, Lactose anhydrous, Gelatin, Talc, Magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Aluminium foil / PVC blisters

Packs of 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Limited
220 Butterfield
Great Marlings
Luton
LU2 8DL
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0522

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2002 / 25/10/2024

10 DATE OF REVISION OF THE TEXT

25/10/2024