

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-amilozide 5 mg/50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg amiloride hydrochloride and 50 mg hydrochlorothiazide.

Excipient with known effect: Also contains Lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

A flat, pale peach bevelled edged tablet bisected on one side, embossed 'BL' on the other.

The tablet can be divided into equal halves

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Potassium-conserving diuretic and antihypertensive.

Co-amilozide 5/50 mg Tablets are indicated in patients with hypertension, congestive heart failure, hepatic cirrhosis with ascites and oedema. In hypertension co-amilozide may be used alone or in conjunction with other anti-hypertensive 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 of therapy. The combination is therefore indicated especially in conditions where potassium balance is particularly important.

4.2 Posology and method of administration

Posology

Adults:*Hypertension*

Initially half a tablet is given once a day. If necessary, increase to one tablet given once a day or in divided doses.

Congestive heart failure

Initially half a tablet a day, subsequently adjusted if required but not exceeding 2 tablets a day. The optimal dose 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.

Hepatic cirrhosis with ascites

Initiate therapy with a low dose. A single daily dose of one tablet may be increased gradually until there is an effective diuresis. Dosage should not exceed 2 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 is contraindicated in children less than 18 years because safety and efficacy have not been established (see section 4.3).

Elderly

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.

Method of administration

For oral administration

4.3 Contraindications

Hypersensitivity to the active substance(s), to any sulfonamide-derived drugs or to any of the excipients listed in section 6.1

Co-Amilozide Tablets 5/50mg are contraindicated if the patient:

- has hyperkalaemia (plasma potassium over 5.5 mmol/l)
- is taking other potassium conserving diuretics or potassium supplements or potassium-rich food (except in severe and/or refractory cases of hypokalaemia under careful monitoring)

- is having concomitant treatment with spironolactone or triamterene
- has anuria
- has acute renal failure or severe progressive renal disease
- has severe hepatic failure or precoma associated with hepatic cirrhosis
- has Addison's disease
- has hypercalcaemia
- has concurrent lithium therapy
- has diabetic nephropathy
- has blood urea over 10 mmol/l, diabetes mellitus, or serum creatinine over 130 µmol/l where serum electrolyte and blood urea cannot be monitored carefully and frequently.
- In renal impairment, use of a potassium-conserving agent may result in rapid development of hyperkalaemia.
- Co-amilozone is not recommended for children under 18 years old.

For use in pregnancy and breast-feeding mothers, see 4.6 'Fertility, 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 or in hospital patients with hepatic cirrhosis or congestive heart failure with renal involvement, who were seriously ill, 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).

Neither potassium supplements nor a potassium-rich diet should be used with Co-amilozone except under careful monitoring in severe and/or refractory cases of hypokalaemia.

Some deaths have been reported in this group of patients.

Treatment of hyperkalaemia: Should hyperkalaemia develop, discontinue treatment immediately and, if necessary, take active measures to reduce the plasma potassium to normal.

Impaired renal function: Renal function should be monitored because the use of Co-amilozone in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine levels fall below 30 ml/min.

Electrolyte imbalance: Although the likelihood of electrolyte imbalance is reduced by Co-amilozide, careful check should be kept for such signs of fluid and electrolyte imbalance as hyponatraemia, hypochloaemic 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 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.

Hypokalaemia may develop, especially as a result of brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalaemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

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.

Azotaemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotaemia and oliguria develop during treatment of renal disease, 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.

Metabolic: Hyperuricaemia may occur, or gout may be aggravated or precipitated in certain patients receiving thiazides. 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-amiloride. 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.

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

Important information regarding the ingredients of this medicine

Lactose:

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

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 prescribing information for lithium preparations before use of such preparations.

Non-Steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 (COX-2) Inhibitors: Non-steroidal anti-inflammatory drugs (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.

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. Therefore, the combination should be administered with caution in patients with compromised renal function. Concomitant administration of NSAIDs and potassium-sparing agents, including amiloride HCl, may cause hyperkalemia, particularly in elderly patients. Therefore, when amiloride HCl is used concomitantly with NSAIDs, serum potassium levels should be carefully monitored.

Amiloride Hydrochloride

When amiloride hydrochloride is administered concomitantly with an angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, trilostane, ciclosporin or tacrolimus, the risk of hyperkalaemia may be increased. 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.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates or narcotics: Co-administration may potentiate orthostatic hypotension. 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. 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. 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. 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. Non-depolarising muscle relaxants such as tubocurarine may possibly interact with Co-amilozide to increase muscle relaxation.

Drug/laboratory tests: Because thiazides may affect calcium metabolism, Co-amilozide may interfere with tests for parathyroid function.

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 toxæmia 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 is excreted in human milk, 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

Infrequently, patients may experience 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**:

General disorders and administration site conditions: anaphylactic reaction, headache *weakness *, fatigue, malaise, chest pain, back pain, syncope

Cardiac Disorders: arrhythmias, tachycardia, digitalis toxicity, orthostatic hypotension, angina pectoris

Gastrointestinal disorders: anorexia *, nausea *, vomiting, diarrhoea, constipation, abdominal pains, GI bleeding, changes in appetite, abdominal fullness, flatulence, thirst, hiccups.

Metabolism and nutrition disorders: elevated plasma potassium levels (above 5.5 mmol/l), electrolyte imbalance, hyponatraemia (see 4.4 'Special warnings and precautions for use'), gout, dehydration, symptomatic hyponatraemia.

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

Skin and subcutaneous tissue disorder: diaphoresis, rash*, pruritus, flushing.

Musculoskeletal and connective tissue disorders: leg ache, muscle cramps, joint pains.

Nervous system disorders: dizziness*, vertigo, paraesthesiae, stupor.

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

Respiratory, thoracic and mediastinal disorders: dyspnoea

Special senses: bad taste, nasal congestion, visual disturbance.

Renal and urinary disorders: impotence, dysuria, nocturia, incontinence, renal dysfunction including renal failure.

Additional side effects that have been reported with the individual components and may be potential side effects of Co-amilozide are listed below:

Amiloride:

General disorders and administration site conditions: neck/shoulder ache, pain in extremities.

Gastrointestinal disorders: abnormal liver function, activation of probable pre-existing peptic ulcer, dyspepsia, jaundice.

Skin and subcutaneous tissue disorder: dry mouth, alopecia.

Nervous system disorders: tremors, encephalopathy.

Blood and lymphatic system disorders: aplastic anaemia, neutropenia.

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

Psychiatric disorders: decreased libido, somnolence.

Respiratory, thoracic and mediastinal disorders: cough.

Special senses: tinnitus, increased intra-ocular pressure.

Renal and urinary disorders: polyuria, urinary frequency, bladder spasm.

Hydrochlorothiazide:

General disorders and administration site conditions: fever.

Cardiac disorders: necrotising angiitis (vasculitis, cutaneous vasculitis).

Gastrointestinal disorders: jaundice (intrahepatic cholestatic jaundice), pancreatitis, cramping, gastric irritation.

Endocrine/Metabolic: glycosuria, hyperglycaemia, hyperuricaemia, hypokalaemia.

Skin and subcutaneous tissue disorder: photosensitivity, sialadenitis, urticaria, toxic epidermal necrolysis.

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

Neoplasm benign, malignant and unspecified (incl cysts and polyps):

Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Psychiatric disorders: restlessness.

Eye disorders: choroidal effusion (frequency not known), transient blurred vision, xanthopsia.

Renal and urinary disorders: interstitial nephritis.

Respiratory, thoracic and mediastinal disorders: respiratory distress, including pneumonitis, pulmonary oedema.

Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

* Side effects that have been reported most frequently during controlled clinical trials with Co-amilozide

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 Website: www.mhra.gov.uk/yellowcard or search in the Google play or Apple App Store.

4.9 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. Emesis should be induced and/or gastric lavage performed. The most common signs and symptoms of overdosage with amiloride hydrochloride are dehydration and electrolyte imbalance. Blood pressure should be monitored and corrected where necessary. If hyperkalaemia occurs, active measures should be taken to reduce the plasma potassium levels.

Electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration are the most common signs and symptoms of hydrochlorothiazide overdosage.

If digitalis has 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 HCTZ 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 HCTZ use (50000mg 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 (~25,000 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

About 70% of an oral dose of hydrochlorothiazide is absorbed. It has a plasma half life of 5.6 to 14.8 hours. It is excreted unchanged in the urine. It crosses the placental barrier and is secreted in breast milk.

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.

5.3 Preclinical safety data

None Known

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Microcrystalline cellulose
Sodium starch glycollate
Purified talc
Magnesium stearate
Sunset yellow (E110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years in Securitainers
4 years in Al/PVC-PVDC blister packs.

6.4 Special precautions for storage

Do not store above 25°C. Store in original package, to protect from light and moisture.

Securitaniers: Keep the container tightly closed.

Blisters: Keep the blister in the outer carton.

6.5 Nature and contents of container

Securitainers stoppered with a polyurethane foam insert and sealed with a press cap.

Pack size: 100 or 500 tablets.

Aluminium/PVC/PVDC blisters consisting of Aluminium sealing foil & Clear PVC/PVDC 250micron/120 GSM forming foil. The Blisters are subsequently packed into cardboard cartons.

Pack size: 28, 50 or 100 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd
Unit 3, Canalside
Northbridge Road
Berkhamsted
Herts
HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0227

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

01/06/2011

10 DATE OF REVISION OF THE TEXT

13/10/2022