SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Amilozide Tablets BP 5/50 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5.68 mg Amiloride Hydrochloride, equivalent to amiloride hydrochloride anhydrous 5.0 mg, and 50 mg Hydrochlorothiazide. For excipients. See 6.1.

3 PHARMACEUTICAL FORM

Tablets
Flat, round, bevel edged tablets, engraved 4K2 on one side, with a breakline on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-amilozide is a potassium-conserving diuretic and an antihypertensive indicated for the treatment of patients with congestive heart failure, hypertension or hepatic cirrhosis with ascites and oedema, particularly where potassium balance is important.

4.2 Posology and method of administration

For oral administration.

Adults  

Hypertension

Usually half a tablet given once a day. The dosage may be increased if necessary 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 two tablets a day. Optimal dosage is determined by the diuretic response and the plasma potassium level. Once an initial diuresis has been achieved, the dosage may be reduced for maintenance therapy, which may be on an intermittent basis.

**Hepatic Cirrhosis with Ascites**

Therapy should be initiated with a low dose, i.e. a single daily dose of 1 tablet which may be gradually increased until there is effective diuresis. The dosage should not exceed two tablets daily. The maintenance dosage may be lower than the dose required to initiate diuresis, therefore, dosage reduction should be attempted when the patient’s weight is stabilised.

**Children**

Co-amilozide is not recommended for use in children.

**The Elderly**

The dosage should be carefully adjusted to renal function and clinical response as the elderly are more susceptible to electrolyte imbalance.

### 4.3 Contraindications

Co-amilozide is contra-indicated in hyperkalaemia (serum potassium over 5.5 mmol/litre); anuria; acute renal failure, severe progressive renal failure; precoma associated with hepatic cirrhosis; severe hepatic failure; Addison’s disease; hypercalcaemia; concurrent lithium therapy; diabetic nephropathy; patients with blood urea over 10 mmol/l; patients with diabetes mellitus or those with serum creatinine over 130 μmol/l in whom serum electrolyte and blood urea levels cannot be monitored carefully and frequently or concomitant use with spironolactone or triamterene. Co-amilozide should not be used in patients receiving other potassium-conserving diuretics, potassium supplements or potassium rich food (unless in severe and/or refractory cases of hypokalaemia under careful monitoring), or those with a known sensitivity to amiloride hydrochloride or hydrochiorothiazide or to other sulphonamide-derived drugs. It is also not recommended for use in children. For use in pregnancy and breast-feeding mothers, see 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 in combination 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 undergoing vigorous
diuretic therapy. Such patients should be carefully observed for clinical, laboratory and ECG evidence of hyperkalaemia (not always associated with abnormal ECG).

Neither potassium nor a potassium rich diet should be used with co-amilozide except with careful monitoring in severe and/or refractory cases of hyperkalaemia. Some deaths have been reported in these patients.

Should hyperkalaemia develop, treatment should be discontinued immediately, and if necessary active measures should be taken to reduce the plasma potassium to normal.

Renal function should be monitored as the use of co-amilozide in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine levels fall below 30 ml/min.

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

Electrolyte imbalance: Although the likelihood of electrolyte imbalance is reduced by coamilozide, careful check should be kept for signs of fluid and electrolyte imbalance such as hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia. If the patient is vomiting excessively or receiving parenteral fluids, it is particularly important to make serum and urine electrolyte determinations.

The warning signs of symptoms of fluid and electrolyte imbalance include: dryness of mouth. weakness, lethargy, drowsiness, restlessness, seizures, 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 sensitise or exaggerate the response of the heart to the toxic effects of digitalis, (eg. increased ventricular irritability).

Diuretic-induced hyponatraemia is usually mild and asymptomatic. 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, and 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. Co-amilozide should be discontinued if increasing azotaemia and oliguria develop during treatment of renal disease.
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 (see 4.3 ‘Contra-indications’), thereby requiring adjustment of antidiabetic agents, including insulin.

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 commencing 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.

There is a possibility that thiazides may activate or exacerbate systemic lupus erythematosus.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of hyperkalaemia may be increased when amiloride hydrochloride is administered concurrently with an ACE inhibitor therefore, if concomitant use is required because of demonstrated hypokalaemia, this should be with caution and with frequent monitoring of serum potassium.

In concurrent administration the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates or narcotics, which may potentiate orthostatic hypotension.

Oral and parental anti-diabetic drugs which may require adjustment of dose.

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 commencing treatment with an ACE inhibitor, to reduce the possibility of first dose hypotension.
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively. When cholestyramine is given 4 hours after the hydrochlorothiazide, the absorption of hydrochlorothiazide is reduced by 30-35%.

Corticosteroids or ACTH may intensify any thiazide induced electrolyte depletion, particularly hypokalaemia.

Pressor amines such as adrenaline may show decreased arterial responsiveness when used with co-amilozone, but this reaction is not enough to preclude their therapeutic usefulness.

Non-polarising muscle relaxants such as tubocurarine may interact with co-amilozone to increase muscle relaxation.

Lithium may accumulate as a result of reduced renal clearance, and add a high risk of lithium toxicity. Reference should be made to the prescribing information for lithium preparations before use of such products.

Non-steroidal anti-inflammatory drugs may attenuate the diuretic natriuretic and anti-hypertensive effects of diuretics. Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride hydrochloride, may cause renal failure and hyperkalaemia, particularly in elderly patients. Therefore, when amiloride hydrochloride is used concomitantly with NSAIDs, serum levels and renal function should be carefully monitored.

Co-amilozone can act synergistically with chlorpropamide to increase the risk of hyponatraemia.

Co-amilozone may interfere with tests for parathyroid function as thiazides may effect calcium metabolism.

### 4.6 Pregnancy and lactation

Co-amilozone is not recommended in pregnancy. Diuretics do not prevent the development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful for its treatment.

Thiazides are excreted in breast milk, therefore, if the drug is deemed essential the patient should stop nursing.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta and their use should be assessed against harm to the foetus where pregnancy is present or suspected. 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 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.

4.7 Effects on ability to drive and use machines

Occasionally, patients may experience fatigue, weakness, stupor, dizziness and vertigo. If these occur, the patient should be warned not to drive or operate machinery.

4.8 Undesirable effects

Minor side effects are relatively common, but more significant effects are infrequent. No increase in the risk of adverse reactions has been observed other than those associated with each of the components themselves. Reported side effects are generally associated with diuresis, thiazide therapy or the underlying disease.

Reported adverse reactions for the combination include:

Headache; weakness; fatigue, malaise, chest pain, back pain, syncope. Arrhythmias, tachycardia, digitalis toxicity, orthostatic hypotension, angina pectoris. Anorexia, nausea, vomiting, diarrhoea, constipation. abdominal pain, GI bleeding, appetite changes. abdominal fullness, flatulence, thirst and hiccups. Elevated plasma protein levels (above 5.5 mmol/l), electrolyte imbalance, hyponatraemia (see 4.4 ‘Special warnings and special precautions for use’), gout, dehydration, symptomatic hyponatraemia. Rash, pruritus, flushing, diaphoresis. Leg ache, muscle cramps, joint pain. Dizziness, vertigo, paraesthesiae, stupor. Insomnia, mental confusion, depression, nervousness, sleepiness. Dyspnoea. Bad taste, visual disturbances, nasal congestion. Impotence, dysuria, nocruria, incontinence, renal dysfunction including renal failure.

Reported adverse reactions of amiloride are:

Neck/shoulder ache and pain in the extremities. Abnormal liver function, activation of probable pre-existing peptic ulcer, dyspepsia, jaundice. Dry
mouth, alopecia, diaphoresis. Tremors, encephalopathy. Aplastic anaemia, neutropenia.

Palpitation, and one person with partial heart block developed complete heart block. Decreased libido, somnolence. Cough. Tinnitus, increased ultra-ocular pressure. Polyuria, urinary frequency, bladder spasm.

The reported adverse reactions of hydrochlorothiazide are:


4.9 Overdose

No specific antidote is available, and it is not known if the drug is dialysable. Treatment should be symptomatic and supportive, co-amilozide should be discontinued and the patient closely monitored. Emesis should be induced and/or gastric lavage performed.

The most common signs and symptoms of amiloride hydrochloride overdosage are dehydration and electrolyte imbalance. Blood pressure should be monitored and corrected if necessary. If hyperkalaemia occurs active measures should be taken to reduce the plasma potassium levels.

The most common symptoms of hydrochlorothiazide overdosage are dehydration and electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia). If digitalis has been administered, hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: CO3A X01 Thiazides, combinations with other drugs. Hydrochlorothiazide, combinations.

Hydrochiorothiazide is a thiazide diuretic; thiazides act directly on the kidney and reduce the reabsorption of electrolytes from the renal tubules increasing the excretion of sodium and chloride ions and consequently water. The excretion of potassium and magnesium is also increased, the excretion of
calcium is reduced. Following oral dosing a response is obtained in approximately 2 hours and diuresis maintained for 6-12 hours.

Amiloride is a mild diuretic which appears to act mainly on the distal renal tubules. It increases the excretion of sodium and chloride and reduces the excretion of potassium. It takes effect 2 hours after dosing and can persist for about 24 hours. Amiloride adds to the natriuretic but diminishes the kaliuretic effects of other diuretics and is frequently combined with thiazides to conserve potassium and reduce the risk of alkalosis.

5.2 Pharmacokinetic properties

About 70% of an oral dose of hydrochlorothiazide is variably but fairly rapidly absorbed from the gastro-intestinal tract. It has an estimated plasma half-life of 5.6 to 14.8 hours. It is excreted unchanged in urine.

Amiloride is incompletely absorbed from the gastro-intestinal tract, bioavailability of about 50% is reported and is reduced by food. It is not bound to plasma proteins and has a half-life of 6-9 hours, but its effects may persist for up to 48 hours after a single dose. It is excreted unchanged by the kidneys in the urine and faeces.

5.3 Preclinical safety data

Preclinical information has not been included because the safety profile of co-amilozide has been established after many years of clinical use. Please refer to section 4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet contains:

Lactose monohydrate  
Maize starch  
Povidone (E1201)  
Magnesium stearate (E572)  
Sunset yellow (E110)

6.2 Incompatibilities

Not applicable.
6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

HDPE containers with caps or child resistant closures in packs of 28, 30, 50, 56, 60, 100, 250, 500 or 1000 tablets.

Blister strips in packs of 10, 28, 30, 56, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road, Hampden Park
Eastbourne, East Sussex, BN22 9AG.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0216

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/02/97

10 DATE OF REVISION OF THE TEXT