SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Amilozide Tablets 5/50mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Lactose – 96 mg

Sunset yellow (E110) – 0.15 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-amilozide Tablets 5/50mg 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.

This product is intended for patients where potassium depletion is anticipated or might be suspected.

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.

Adults

Hypertension

Initially one tablet given once a day. The dosage may be increased if necessary to two tablets given once a day or in divided dose.

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 tablet a day, subsequently adjusted if required, but not exceeding four tablets a day. Optimal dosage is determined by the diuretic response and the plasma potassium level. Once 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 dose of two tablets may be increased gradually until there is an effective diuresis. Dosage should not exceed

four tablets a day. A gradual weight reduction is especially desirable in cirrhotic patients to reduce the likelihood of untoward reactions associated with diuretic therapy. Maintenance dosages may be lower than those required to initiate diuresis; dosage reduction should therefore be attempted when the patient's weight is stabilised.

Paediatric population

Co-amilozide is not recommended for children under 18 years of age as safety and efficacy has not been established.

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 (see section 4.4).

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substances or other sulphonamide-derived drugs, or to any of the excipients listed in section 6.1
- Hyperkalaemia (plasma potassium over 5.5mmol/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

Co-amilozide is not recommended for use in children under 18 years old.

4.4 Special warnings and precautions for use

Hyperkalaemia: Hyperkalaemia has been observed in patients receiving amiloride hydrochloride, either alone or with other diuretics, particularly in the elderly 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, co-amilozide 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 30 ml/min.

Electrolyte imbalance and blood urea increases: Although the likelihood of electrolyte imbalance is reduced by co-amilozide, 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.

Warnings signs and symptoms of fluid and 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. If the patient is vomiting excessively or receiving parenteral fluids, serum and urine electrolytes should be determined (see section 4.8).

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 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, 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 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 section 4.3). Uraemia may be precipitated or increased by hydrochlorothiazide. Co-amilozide 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 (see section 4.8). Use in severe hepatic failure is contraindicated (see section 4.3).

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

Thiazides may impair glucose tolerance. Diabetes mellitus may be precipitated or aggravated by therapy with co-amilozide (see section 4.3). Dosage adjustment of antidiabetic agents, including insulin, may be required.

Co-amilozide 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.

Concomitant use of medicinal products known to cause hyperkalaemia with hydrochlorothiazide may result in severe hyperkalaemia.

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.

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

This medicine contains Sunset yellow (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Thiazides may decrease urinary calcium excretion, or 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.

Cholestyramine and colestipol reduce the absorption of thiazides and should therefore be given at least 2 hours apart.

Thiazides may impair glucose tolerance. Diabetes mellitus may be precipitated or aggravated by co-amilozide therapy. Dosage adjustment of antidiabetic agents including insulin may be required.

NSAIDs may reduce the diuretic effects of diuretics. However diuretics increase the risk of nephrotoxicity of NSAIDs. Indomethacin and possibly other NSAIDs may increase the risk of hyperkalaemia when taken with potassium sparing diuretics.

Co-amilozide should not be used concomitantly with spironolactone or triamterene.

The risk of hyperkalaemia and an enhanced hypotensive effect may occur if an ACE inhibitor or angiotensin-II antagonist are administered concurrently with amiloride hydrochloride. If concomitant use of these agents is desirable, frequent monitoring of serum potassium should be carried out. There is also an increased risk of hyperkalaemia if cyclosporin, potassium salts or trilostane are used concomitantly with amiloride.

Co-administration of alcohol, barbiturates or narcotics may potentiate orthostatic hypotension. There is a risk of postural hypotension when taken with tricyclic antidepressants. Other antihypertensive agents may have an additive effect; their dosages may need to be reduced (especially adrenergic blockers) when co-amilozide is added to existing therapy.

Diuretic therapy should be discontinued for 2-3 days before an ACE inhibitor is introduced to minimise the risk of a first-dose hypotensive effect. There is an increase in the risk of first dose hypotensive effects when post-synaptic alphablockers, such as prazosin, are taken comitantly with co-amilozide.

Anti-hypertensives, calcium channel blockers, alprostadil, betablockers and moxisylyte can all enhance the antihypertensive effects of co-amilozide tablets.

There is an increased risk of toxicity from cardiac glycosides and the following anti-arrythmics; amiodarone, disopyramide, flecainide and quinidine, if hypokalaemia occurs with a thiazide diuretic. The actions of lidocaine and mexiletine are antagonised by hypokalaemia.

There is an increased risk of hypokalaemia if co-amilozide tablets are taken with the following; reboxetine, amphotericin and high doses of sympathomimetics. There is also an increased risk of hypokalaemia if loop diuretics, thiazides or acetazolamide are given together.

Carbenoxolone can increase the risk of hypokalaemia whilst antagonising the diuretic effect of co-amilozide. The ulcer healing effect of carbenoxolone is antagonised by amiloride.

Corticosteroids or ACTH may intensify any thiazide induced electrolyte depletion, especially hypokalaemia and also antagonise the diuretic effect.

Hypokalaemia and other electrolyte imbalances can lead to an increase in ventricular arrhythmia when co-amilozide is taken with terfenadine, halofantrine, pimozide and sotalol.

Pressor amines, such as adrenaline, may show decreased arterial responsiveness when used with co-amilozide but the therapeutic effect may still be of use.

There is an increased risk of hypercalcaemia if thiazides are given with vitamin D, toremifene or calcium salts.

The diuretic effect of co-amilozide tablets is antagonised by oestrogen, combined oral contraceptives.

Non-depolarising muscle relaxants, such as tubocurarine, may possibly interact with co-amilozide to cause increased muscle relaxation. Other muscle relaxants such as baclofen and tizanidine may enhance the hypotensive effects of co-amilozide.

Lithium may accumulate due to reduced renal clearance.

Hydrochlorothiazide may decrease arterial responsiveness to pressor amines such as noradrenaline (norepinephrine), but not enough to preclude their therapeutic usefulness.

Cisplatin and co-amilozide can increase the risk of nephrotoxicity and ototoxicity.

Co-amilozide combined with chlorpropamide, carbemazapine or aminoglutethimide can act in synergy to increase the risk of hyponatraemia.

Hydrochlorothiazide increases plasma concentrations of fluconazole.

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 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, 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

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

4.8 Undesirable effects

Although minor side effects are relatively common, serious 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:

Appetite changes, anorexia, gout, dehydration

Electrolyte balance:

Elevated plasma potassium levels (above 5.5 mmol/l) electrolyte imbalance, hyponatraemia, (see section 4.4) 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.

Psychiatric disorders:

Insomnia, nervousness, mental confusion, depression

Nervous system disorders:

Headache, dizziness, sleepiness, syncope, paraesthesia, 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 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, thirst

Injury, poisoning and procedural complications:

Digitalis toxicity (see section 4.5)

Amiloride:

Blood and lymphatic system disorders:

Aplastic anaemia, neutropenia

Metabolism and nutrition disorders:

Hyperkalaemia (see section 4.3 and 4.4)

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 (incl cysts and polyps)

Frequency not known (cannot be estimated from the available data): Non-melanoma skin cancer (Basel 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 4.5).

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 section 4.3). 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.

Choroidal effusion (frequency not known: cannot be estimated from the available data)

Vascular disorders:

Necrotising angiitis, vasculitis

Respiratory, thoracic and mediastinal disorders:

Respiratory distress including pneumonitis, pulmonary oedema

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

Frequency unknown: Pemphigoid.

Renal and urinary disorders:

Interstinal 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 (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 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

Symptoms

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 arrythmias.

Management

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 plasma potassium levels.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Low-ceiling diuretics and potassium-sparing agents

ATC code: C03EA01

Amiloride

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

Hydrochlorothiazide

A diuretic which 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 cases 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 (~25,000 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

Amiloride hydrochloride is incompletely absorbed from the gastrointestinal tract bioavailability of about 50% is reported. Food reduces the absorption. It is not significantly bound to plasma proteins and has a half-life of 6-9 hours.

It is excreted unchanged by the kidneys.

Hydrochlorothiazide is rapidly absorbed from the gastro-intestinal tract, with a bioabsorbability of 65-70%. It has a plasma half-life of about 5 hours with a terminal half-life of up to 15 hours. It is excreted unchanged by the kidneys. Hydrochlorothiazide crosses the placental barrier and is excreted in breast milk.

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

None known.

6.3 Shelf life

5 years in Securitainers and 4 years in blister packs.

6.4 Special precautions for storage

Store below 25°C. Protect from moisture and light.

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 blisters in cardboard cartons. Pack size: 28, 50 or 100 tablets.

6.6 Special precautions for disposal

None given.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0032

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