1. NAME OF THE MEDICINAL PRODUCT

Co-amilofruse Tablets 5/40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains furosemide 40mg and anhydrous amiloride hydrochloride 5mg

Excipient with known effect
Sunset yellow aluminium lake (E110)
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

A pale orange film-coated biconvex tablet marked “CF” breakline “5/40” on one side and “G” on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Co-amilofruse tablets are indicated where a prompt diuresis is required. It is of particular value in conditions where potassium conservation is important; congestive cardiac failure, nephrosis, corticosteroid therapy, oestrogen therapy. Ascites associated with cirrhosis.

4.2 Posology and method of administration

For oral administration

Adults: One or two tablets to be taken in the morning.

Children: Not recommended for children under 18 years of age as safety and efficacy have not been established.

Elderly: The dosage should be adjusted according to diuretic response; serum electrolytes and urea should be carefully monitored.

4.3 Contraindications

Hypersensitivity to furosemide, amiloride, sulphonamides or sulphonamide derivatives, or to any of the excipients of the product.
Patients with hypovolaemia or dehydration (with or without accompanying hypotension)
Patients with impaired renal function and a creatinine clearance below 30ml/min 1.73m^2 body surface area, anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma, hyperkalaemia, severe hypokalaemia, severe hyponatraemia, concomitant potassium supplements or potassium sparing, precomatose states associated with cirrhosis, Addison's disease, and breast feeding women.

Co-amilofruse is contraindicated in children and adolescents under 18 years of age as safety in this age group has not yet been established.

4.4 Special warnings and precautions for use

Co-amilofruse should be discontinued before a glucose tolerance test.

Co-amilofruse should be used in caution in elderly patients or those with potential obstruction of the urinary tract or disorders rendering electrolyte balance precarious.

Urinary output must be secured. Patients with partial obstruction of urinary flow, (e.g. in prostatic hypertrophy, impairment of micturition), are at increased risk of developing acute urinary retention and require careful monitoring.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy with co-amilofruse (see section 4.3).

Particularly careful monitoring is necessary in elderly or seriously ill patients and those with:

- Hypotension
- those at risk from a pronounced fall in blood pressure.
- Patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase
- Gout
- Patients with hepatic cirrhosis together with impaired renal function
- Patients with hypoproteinaemia e.g. associated with nephrotic syndrome (the therapeutic effect of furosemide may be reduced and its ototoxicity potentiated (see also section 4.8). Cautious dose titration is required.

Caution should be observed in patients liable to electrolyte deficiency. Regular monitoring of serum sodium, potassium, creatinine and glucose is generally recommended during therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Co-amilofruse.

Frequent checks of the serum potassium level are necessary in patients with impaired renal function and a creatinine clearance below 60ml/min per 1.73m^2 body surface area as well as in cases where Co-amilofruse is taken in combination with certain other drugs which may lead to an increase in potassium levels.

In patients who are at high risk for radiocontrast nephropathy, furosemide is not recommended to be used for diuresis as part of the preventative measures against radiocontrast induced nephropathy.

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

Concomitant use with risperidone:
In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.
No pathophysiological mechanism has been identified to explain this finding and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (See section 4.3 Contraindications).

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

Co-amilofruse contains Sunset yellow aluminium lake (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The dosage of concurrently administered cardiac glycosides, diuretics, anti-hypertensive agents, or other drugs with blood pressure lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with Co-amilofruse. A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors or angiotensin II receptor antagonists are added to furosemide therapy, or their dose level increased. The dose of Co-amilofruse should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitor or angiotensin II receptor antagonist or increasing their dose.

When amiloride is taken in combination with potassium salts, with drugs which reduce potassium excretion, with non-steroidal anti-inflammatory drugs or with ACE inhibitors, an increase in serum potassium concentration and hyperkalaemia may occur.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as furosemide.

Sucralfate decreases the intestinal absorption of furosemide, and should not be taken within two hours of co-amilofruse.

As with other diuretics, serum levels of lithium may be increased with concomitant use of furosemide, resulting in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Patients should be carefully monitored, and the lithium dosage adjusted if necessary.

Risperidone: Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use. See section 4.4 Special warnings are precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Certain NSAIDs (e.g. indomethacin, acetylsalicyclic acid) may attenuate the action of co-amilofruse and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylic toxicity may be increased by furosemide. Co-amilofruse may sometimes attenuate the effects of other drugs (e.g. anti-diabetics and pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).

Furosemide may potentiate the ototoxicity of aminoglycoside antibacterials and other ototoxic drugs. Since damage may be irreversible, co-administration of co-amilofruse should be avoided if possible.

There is a risk of ototoxicity if cisplatin and furosemide are given concurrently. In addition, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Amiloride may cause raised blood digoxin levels. Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT prolongation syndrome).

Attenuation of the effect of Co-amilofruse may occur following concurrent administration of phenytoin.

Concomitant administration of carbamazepine or aminogluthethimide may increase the risk of hyponatraemia.

Corticosteroids administered concurrently may cause sodium retention.

Corticosteroids, carbenoxolone, liquorice, B_2 sympathomimetics in large amounts, and prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

Probenecid, methotrexate and other drugs which, like Co-amilofruse undergo significant renal tubular secretion may reduce the diuretic effect of co-amilofruse. In turn furosemide may decrease the renal elimination of such drugs. In case of high dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels, and an increased risk of adverse events due to furosemide, and the concurrent medication.

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis.

4.6 Fertility, pregnancy and lactation

Pregnancy

Results of animal work, in general show no hazardous effects of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, furosemide crosses the placental barrier. It must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

The safety of amiloride hydrochloride has not been established and is therefore not recommended for use during pregnancy.

Lactation

Furosemide passes into breast milk and may inhibit lactation. It is not known whether amiloride hydrochloride is excreted in breast milk. Breast-feeding must be avoided during treatment with Co-amilofruse.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000;<1/100); rare (≥1/10,000;<1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Co-amilofruse Tablets 5/40 mg are generally well tolerated.

Blood and lymphatic system disorders
Frequency not known:
Eosinophilia.

Occasionally thrombocytopenia may occur. In rare cases, leucopenia and, in isolated cases agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

Nervous system disorders
Frequency not known:
Paraesthesia may occur.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).

Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension).

Metabolism and nutrition disorders
Frequency not known:
Serum calcium levels may be reduced; in very rare cases tetany has been observed.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months.

Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest.

As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Furosemide leads to increased excretion of sodium and chloride and consequently water. In addition excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. However, as treatment is continued, the serum potassium concentration may increase due to the later onset of action of amiloride, especially in patients with impaired renal function. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses, although amiloride may contribute to the development or aggravation of metabolic acidosis. Warning signs of electrolyte disturbances include increased thirst, headache, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Disturbances of electrolyte balance, particularly if pronounced, must be corrected. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment. Pseudo-Bartter syndrome may occur in the context of misuse and/or long-term use of furosemide.

The diuretic action of furosemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients.

As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

Ear and labyrinth disorders
Frequency not known:
Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. nephrotic syndrome) and/or when intravenous furosemide has been given too rapidly.

Frequency uncommon:
Cases of deafness, sometimes irreversible, have been reported after administration of furosemide.

Vascular disorders
Frequency not known:
Furosemide may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance.

Hepatobiliary disorders
Frequency not known:
In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Skin and subcutaneous tissue disorders
Frequency not known:
The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis, or shock is very low, but when these occur treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, bullous pemphigoid, exfoliative dermatitis, purpura, Stevens Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms).

Psychiatric disorders
Frequency not known:
Rare complications may include minor psychiatric disturbances.

Renal and urinary disorders
Frequency not known:
Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur. For example, in patients with bladder emptying disorders, prostatic hyperplasia or narrowing of the urethra.

Nephrocalcinosis/nephrolithisasis has been reported in infants.

Reproductive system and breast disorders
Frequency not known:
If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Immune system disorders
Frequency not known:
Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.

Exacerbation or activation of systemic lupus erythematosus.

Gastrointestinal disorders
Frequency not known:
Side-effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) and constipation may occur but are not usually severe enough to necessitate withdrawal of treatment.

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.

4.9 Overdose

Treatment of overdosage should be aimed at reversing dehydration and correcting electrolyte imbalance, particularly hyperkalaemia. Emesis should be induced or gastric lavage performed. Treatment should be symptomatic and supportive.

If hyperkalaemia is seen, appropriate measures to reduce serum potassium must be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

High ceiling diuretics and potassium-sparing agents. C03E B01

Furosemide
Furosemide is a potent diuretic with a rapid action. Its effects are evident within 1 hour after a dose by mouth and lasts for about 4-6 hours. After iv injection, its effects are evident in about 5 minutes and last for about 2 hours. It has been reported to exert inhibiting effects on electrolyte re-absorption in the proximal and distal renal tubules and in the ascending loop of Henle. Excretion of sodium, potassium and chloride ions is increased and water excretion enhanced. It has no effect on carbonic anhydrase. Furosemide is used similarly to chlorothiazide and may be effective in patients unresponsive to thiazide diuretics. It is also used in the treatment of renal insufficiency and, where appropriate, in forced diuresis regimens for the management of poisoning with some drugs, such as the barbiturates.

Furosemide has a steep dose response curve, which gives it a wide therapeutic range.

Amiloride HCI
Amiloride is a mild diuretic which appears to act mainly on the distal renal tubules. It takes effect about 2 hours after administration by mouth and its diuretic action has been reported to persist for about 24 hours. The full effect may be delayed until alter several days of treatment. Like spironolactone, it increases the excretion of sodium and chloride and reduces the excretion of potassium. Unlike spironolactone, however, it does not appear to act by inhibiting aldosterone. Amiloride does not inhibit carbonic anhydrase.

Amiloride adds to the natriuretic but diminishes the kaliuretic effects of other diuretics, and is mainly used as an adjunct to the thiazides, furosemide and similar diuretics, to conserve potassium in the treatment of refractory oedema associated with hepatic cirrhosis and congestive heart failure. It has little effect in the treatment of hypertension.

5.2. Pharmacokinetic properties

Furosemide
Furosemide is incompletely but fairly rapidly absorbed from the gastro-intestinal tract. It has a biphasic half-life in the plasma with a terminal elimination phase that has been estimated to range up to about 1½ hours. it is up to 99% bound to plasma proteins, and is mainly excreted in the urine, largely unchanged, but also in the form of glucuronide and free amine metabolites. Variable amounts are also excreted in the bile, non-renal elimination being considerably increased in renal failure. Furosemide crosses the placental barrier and is excreted in milk.

Amiloride
Amiloride is incompletely absorbed from the gastro-intestinal tract; peak serum concentrations are achieved about 3 or 4 hours after administration by mouth. It is excreted unchanged in the urine and animal studies have shown little evidence of any biliary excretion. Amiloride has been estimated to have a serum half-life of about 6 hours.

5.3. Pre-clinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Mannitol
Pregelatinised Maize Starch
Povidone
Maize Starch
Colloidal Anhydrous Silica (Aerosil)
Purified Talc
Magnesium Stearate
Sodium Starch Glycollate (Explotab)

Film Coating
Opadry Orange 8729 composed of:
- Hydroxypropylmethylcellulose 2910
- Titanium Dioxide El 71
- Polyethylene Glycol 400
- Sunset Yellow Aluminium Lake (El 10) and
- Quinoline Yellow Aluminium Lake (E104)

Purified Water
Carnauba Wax

6.2. Incompatibilities

Not applicable.

6.3. Shelf-Life

2 years.

6.4. Special Precautions for Storage

Store below 25°C. Protect from light.

6.5. Nature and Content of Container

Polypropylene tablet container with polyethylene cap with optional polyethylene ullage filler, pack sizes of 50, 100. 250 and 500 tablets.

Al (20µm)/PVdC (unplasticised 285µm) blister, pack sizes of 28 or 56 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for Use/Handling

No specific instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0054

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06th November 1997

10. DATE OF PARTIAL REVISION OF THE TEXT

January 2005.

10 DATE OF REVISION OF THE TEXT

05/06/2017