SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Amilofruse 2.5/20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of Amiloride Hydrochloride (dihydrate) and 20mg of Furosemide.

Excipient(s) with known effect
Contains Lactose 42.100 mg, sunset yellow 0.100 mg and sodium 0.198 mg.
For a full list of excipients, see section 6. 1.

3 PHARMACEUTICAL FORM

Tablets for oral use.

Pale orange circular, flat faced beveled edge tablets, debossed with ARD | 20 on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-Amilofruse is a potassium sparing diuretic which is indicated where a prompt diuresis is required. It is of particular value in conditions where potassium conservation is important: congestive cardiac failure, nephrosis, fluid retention due to corticosteroid or oestrogen therapy and ascites associated with cirrhosis.

4.2 Posology and method of administration

Posology

Adults

One or two tablets to be taken in the morning.

Paediatric population

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.

Method of administration

Oral administration.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or sulphonamides or sulphonamide derivatives.

Patients with hypovolaemia or dehydration (with or without accompanying hypotension). Patients with an impaired renal function and a creatinine clearance below 30ml/min per 1.73 m^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 diuretics, precomatose states associated with cirrhosis, Addison's disease and breast feeding women.

Co-Amilofruse is contraindicated in children and adolescents less than 18 years of age, as safety in this age group has not been established.

4.4 Special warnings and precautions for use

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

Co-Amilofruse Tablets should be used with particular 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 outflow, for example patients with prostatic hypertrophy or impairment of

micturition have an increased risk of developing acute retention and require careful monitoring.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Particularly careful monitoring is necessary in:

- patients with hypotension.
- patients who are 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.
- patients with gout.
- patients with hepatic cirrhosis together with impaired renal function.
- patients with hypoproteinaemia, e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

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.

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
May cause allergic reactions.

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

Important information on sodium content
This medicine contains less than 1 mmol sodium (23 mg) per each tablet, that is to say essentially 'sodium-free'.

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 nonsteroidal 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.

Oral Co-Amilofruse and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with Co-Amilofruse, resulting in increased

lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

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 and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Certain non-steroidal anti-inflammatory agents (e.g. indometacin, acetylsalicylic 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. the effects of anti-diabetics and of pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).

Furosemide may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with Co-Amilofruse if there are compelling medical reasons.

There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg 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 interval prolongation syndrome).

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

Concomitant administration of carbamazepine or aminoglutethimide 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 furosemide, undergo significant renal tubular secretion may reduce the effect of Co-Amilofruse. Conversely, furosemide may decrease renal elimination of these 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 effects due to furosemide or the concomitant 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.

Aliskiren reduces the plasma concentration of furosemide given orally. Reduced effect of furosemide might be observed in patients treated with both aliskiren and oral furosemide, and it is recommended to monitor for reduced diuretic effect and adjust the dose accordingly.

4.6 Fertility, pregnancy and lactation

Pregnancy
Results of animal work, in general, show no hazardous effect 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.

Breast-feeding
Furosemide passes into breast milk and may inhibit lactation. It is not known whether Amiloride Hydrochloride is excreted in breast milk. Breastfeeding must be avoided during treatment with Co-Amilofruse.

4.7 Effects on ability to drive and use machines

None known.

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 are generally well tolerated.

Blood and lymphatic system disorders
Frequency not known:
Eosinophilia, haemoconcentration.

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.

Nervous system disorders
Frequency not known:
Paraesthesia may occur.

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

Dizziness, fainting, loss of consciousness and headache.

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

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

Glucose tolerance may be impaired 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. The serum potassium concentration may decrease, especially at the commencement of treatment owing to the earlier onset action of furosemide. 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. Electrolyte disturbances (including symptomatic) 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 increases in blood creatinine and blood uric acid, hyponatremia, hypochloremia, hypokalaemia, attacks of gout, hypocalcemia, hypomagnesemia and increased blood urea.

Ear and labyrinth disorders
Frequency not known:

Hearing disorders, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

Tinnitus

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 (hypotension) 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.

Thrombosis

Vasculitis

Hepato-biliary disorders
Frequency not known:
In isolated cases, cholestasis and transaminases increases may develop.

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

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

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

Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

Tubulointerstitial nephritis

Renal failure

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 the treatment.

Pancreatitis acute

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

4.9 Overdose

Treatment of 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

Pharmacotherapeutic group: furosemide and potassium-sparing agents,
ATC code: CO3EB01

FUROSEMIDE:
Furosemide is a potent loop diuretic which acts primarily to inhibit electrolyte reabsorption in the thick ascending loop of Henle. Excretion of sodium, potassium and chloride ions is increased and water excretion enhanced.

AMILORIDE:
Amiloride is a mild diuretic which moderately increases the excretion of sodium and chloride and reduces potassium excretion, and appears to act mainly on the distal renal tubules. It does not appear to act by inhibition of aldosterone and does not inhibit carbonic anhydrase. Amiloride adds to the natriuretic but diminishes the kaliuretic effects of other diuretics.

A combination of Furosemide and Amiloride is a diuretic which reduces the potassium loss of furosemide alone while avoiding the possible gastro-intestinal disturbances of potassium supplements.

5.2 Pharmacokinetic properties

Furosemide:

Approximately 65% of the dose is absorbed after oral administration. The plasma half-life is biphasic with a terminal elimination phase of about 1½ hours. Furosemide is up to 99% bound to plasma proteins, and is mainly excreted in the urine, largely unchanged, but also excreted in the bile, non-renal elimination being considerably increased in renal failure. Furosemide crosses the placental barrier and is excreted in the milk.

Amiloride:

Approximately 50% of the dose is absorbed after oral administration and peak serum concentrations are achieved by three to four hours. The serum half-life is estimated to be about 6 hours. Amiloride is not bound to plasma proteins. Amiloride is not metabolised and is excreted unchanged in the urine.

Pharmacokinetic studies have been completed on Co-Amilofruse Tablets.

FUROSEMIDE:

Cp MAX = 1/14 µg/ml SD = 0.67

Tmax = 3.0 hours

AUC = 3.17µg/ml hr SD = ± 1.25

AMILORIDE:

Cp MAX = 13.42 ng/ml SD = 5.74

Tmax = 4.0 hours

AUC = 154 ng/ml hr SD = ± 65.2

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline Cellulose
Sunset Yellow FCF Lake (E110)
Povidone K30
Sodium Starch Glycollate
Magnesium Stearate

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.Store in the original package. Keep the containers tightly closed.

6.5 Nature and contents of container

Opaque white blister packs manufactured from UPVC and aluminium foil containing 28, 30, 56, or 60 tablets.

Polypropylene or polyethylene containers with a lid containing 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
Ares Block
Odyssey Business Park
West End Road
South Ruislip
HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0654

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/03/2009

10 DATE OF REVISION OF THE TEXT

23/06/2025