

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fruco 40 mg/5 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains furosemide 40mg and amiloride hydrochloride equivalent to 5mg of anhydrous amiloride hydrochloride.

Each tablet also contains lactose monohydrate 60 mg and sunset yellow (E110) 0.4 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Round orange flat, bevelled tablet, coded 'Fruco' and a breakline on one face, plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Uses: In the management of fluid retention where potassium conservation is desirable.

4.2 Posology and method of administration

Posology

Adults:

The usual adult dose is 1 tablet (40 mg furosemide and 5 mg amiloride) in the morning. This may be increased to 2 tablets if the initial response is unsatisfactory. In this case it is best to divide the dosage into two daily doses, one to be taken in the morning and the other at noon.

Geriatric population:

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

Extreme care should be taken with dosage in the elderly as this group are more susceptible to serious side effects associated with electrolyte disturbances.

Paediatric population:

There is no relevant use of Fruco in the paediatric population.

Method of administration

The route of administration is oral.

The tablets are to be swallowed whole with sufficient amounts of liquid (approx. half a glass). They are best taken on an empty stomach. The lowest possible dose should be used for treatment.

4.3 Contraindications

- Use in patients with Addison's disease.

- Use in patients hypersensitive to the active ingredients, furosemide, amiloride, sulfonamides or sulfonamide derivatives, or to any of the excipients listed in section 6.1. Patients allergic to sulfonamides may show cross-sensitivity to furosemide.
- Use during pregnancy.
- In breast-feeding women.
- Use in children.
- Use in patients with impaired renal function and a creatine clearance below 30 ml/min per 1.73 m² body surface area, acute renal failure or anuria.
- Use in patients with hyperkalemia.
- Use in patients with severe hypokalemia, however if hypokalemia develops during treatment it can usually be corrected without interrupting treatment.
- Use in patients with hypovolemia or dehydration.
- In patients with severe hyponatraemia.
- In patients with pre-comatose and comatose states associated with hepatic encephalopathy.
- Electrolyte imbalance.
- Concomitant use with potassium supplements (see Interactions with other medicines).

4.4 Special warnings and precautions for use

Patients who are being treated with this preparation require regular supervision, with monitoring of fluid and electrolyte states to avoid excessive loss of fluid. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected.

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.

Fruco should only be used with particular caution in elderly patients or those with potential obstruction of the urinary tract or disorders rendering electrolyte balance precarious. Urinary outflow must be secured. In patients with a partial obstruction of urinary outflow (e.g. in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), increased production of urine may provoke or aggravate complaints. Thus, these patients require careful monitoring- especially during the initial stages of treatment.

Furosemide may induce hyperglycaemia, particularly in patients with latent diabetes, and may require adjustment of dose of hypoglycaemic agents in diabetes mellitus. Regular monitoring of blood glucose levels is recommended.

Furosemide may induce hyperuricaemia and gout.

Ototoxicity may occur if given concomitantly with ototoxic drugs (see Section 4.5).

Bone marrow depression occasionally complicates treatment necessitating withdrawal of the product. The haemopoietic state should therefore be regularly monitored during treatment.

Hyponatraemia, hypochloraemia and raised blood urea nitrogen may occur during vigorous diuresis, especially in seriously ill patients. Careful monitoring of serum electrolytes and urea should therefore be undertaken in these patients.

Hyperkalaemia has been observed in patients receiving amiloride hydrochloride.

Particularly careful monitoring is necessary:

- In patients with hypotension
- In patients who would be at particular risk from an undesirably pronounced fall in blood pressure
- In patients with hepatic cirrhosis together with impaired renal function (hepatorenal syndrome)
- In 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.

Frequent checks of serum potassium levels are necessary in patients with impaired renal function and a creatine clearance below 60 ml/min per 1.73 m² body surface area as well as in cases where treatment is taken in combination with certain other drugs which may lead to an increase in potassium concentration.

Regular monitoring of serum sodium, potassium and creatinine and blood glucose is generally recommended during Fruco therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss (e.g. due to vomiting, diarrhoea or intense sweating). Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Fruco. See section 4.3.

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 when compared to patients treated with risperidone alone or furosemide alone. Caution should be exercised and the risks and benefits of this combination or co-treatment should be considered prior to the decision to use. Dehydration should be avoided. See section 4.5.

Fruco should be discontinued before a glucose tolerance test.

The dosage of concurrently administered cardiac glycosides or antihypertensive agents may require adjustment (see Section 4.5).

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

This product contains sunset yellow (E110), which may cause allergic reactions in some people.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions:

Not recommended associations:

Furosemide may potentiate the damaging effects on hearing of aminoglycosides and other ototoxic drugs. As such hearing disorders may be irreversible, those drugs and Fruco must only be used concurrently in cases where there are compelling medical reasons.

Isolated cases have been described in which intravenous administration of furosemide within 24 hours after taking chloral hydrate has been followed by sensations of heat, sweating attacks, restlessness, nausea, rises in blood pressure and tachycardia. Such a reaction might also occur with Fruco.

Concomitant administration of potassium supplements may cause severe hyperkalaemia and is contra-indicated (see Contraindications).

Precautions for use:

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 and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Fruco decreases the excretion of lithium salts. This may lead to increased serum lithium levels resulting in increased risk of lithium toxicity, including cardiotoxic and neurotoxic effects of lithium. Therefore it is recommended that lithium levels be carefully monitored when patients are receiving concurrent treatment with lithium salts.

Fruco and sucralfate must not be taken simultaneously or separately within 2 hours of each other, because sucralfate decreases the absorption of the furosemide component from the intestine.

Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including renal failure, especially when an ACE inhibitor or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose.

Consideration must be given to interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor or angiotensin II receptor antagonist.

Take into account:

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 potassium concentration and hyperkalaemia may occur.

Concurrent administration of nonsteroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the effect of Fruco. In patients with dehydration or pre-existing hypovolaemia, non steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by furosemide.

Corticosteroids, carbenoxolone, liquorice in larger amounts and prolonged use of laxatives may promote the development of hypokalaemia.

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

Amiloride may cause raised blood digoxin levels, in addition, the effects and side effects of digitalis preparations and drugs inducing QT interval prolongation syndrome may be potentiated by changes in electrolyte concentrations due to furosemide.

Phenytoin may weaken the action of Fruco.

If other antihypertensives, diuretics, or drugs which can lead to a reduction in blood pressure are taken concurrently with Fruco, a more pronounced fall in blood pressure must be anticipated.

The effects of antidiabetic drugs and blood-pressure-increasing sympathomimetics may be weakened, while the effects of curare-type muscle relaxants or of theophylline may be potentiated.

The harmful effects of nephrotoxic drugs on the kidney may be potentiated by furosemide.

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

Concomitant use of cyclosporine A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperuricemia and cyclosporine impairment or renal urate excretion.

Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide.

Patients who were at high risk for radiocontrast nephropathy treated with furosemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

Risperidone: Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide should be considered prior to the decision to use (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Fruco must not be taken during pregnancy.

Breast-feeding

Breast-feeding while taking Fruco must be avoided.

4.7 Effects on ability to drive and use machines

During treatment the powers of concentration and reaction may be impaired, affecting the patient's ability for example, to drive or to operate machinery. This applies especially at the commencement of treatment or after consumption of alcohol.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

Renal & Urinary Disorders

Common: Acute retention of urine in patients with a partial obstruction of urinary outflow may in extreme cases lead to acute retention of urine with overdistension of the bladder.

Rare: Interstitial nephritis and nephrocalcinosis/nephrolithiasis in premature infants may also occur.

Metabolism & Nutrition Disorders

Common: Fruco causes increased excretion of water and certain electrolytes (e.g. sodium, calcium, magnesium, and chloride). The serum potassium concentration may decrease, especially at the commencement of treatment. Particularly as treatment is continued, the potassium concentration may increase, especially in patients with impairment of renal function.
Hyperuricaemia and precipitation of acute gout may occur.

Rare: Treatment with Fruco may lead to increases in blood creatinine and urea levels and in blood lipids (e.g. cholesterol and triglycerides). The blood concentration of uric acid may increase and may lead to attacks of gout.

Disturbances in electrolyte balance may produce various symptoms (e.g. increased thirst, headache, confusion, muscle cramps, tetany, muscle weakness and disorders of cardiac rhythm, or even gastrointestinal symptoms). In the event of an irregular pulse, tiredness or muscle weakness, the possibility of hyperkalaemia in particular must be considered.

Furosemide may contribute to the development or aggravation of metabolic alkalosis, as may amiloride to the development or aggravation of metabolic acidosis.

Disturbances in electrolyte balance – particularly if pronounced – must be corrected.

The diuretic action may lead or contribute to hypovolaemia and dehydration. To avert these it is important to compensate any undesired losses of fluid.

Glucose tolerance may decrease during treatment with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control. Latent diabetes may become manifest for the first time.

Gastrointestinal Disorders

Rare: Gastrointestinal symptoms such as nausea, vomiting or diarrhoea may occur.

Very rare: In isolated cases, acute pancreatitis may develop.

Hepato-Biliary Disorders

Very rare: Intrahepatic cholestasis and an increase in liver transaminases may occur.

Ear & Labyrinth Disorders

Uncommon: Deafness (sometimes irreversible).

Rare: Hearing disorders and tinnitus although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephrotic syndrome). Ototoxicity may occur.

Skin & Subcutaneous Tissue Disorders

Uncommon: Reactions (e.g. allergic) involving the skin and mucous membranes may occasionally be encountered; these may manifest themselves in various forms including itching, urticarial and other skin rashes or bullous skin lesions, erythema multiforme, bullous pemphigoid, exfoliative dermatitis, purpura, photosensitivity and DRESS (Drug rash with eosinophilia and systemic symptoms).

Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalised exanthematous pustulosis).

Immune System Disorders

Rare: Severe anaphylactic or anaphylactoid reactions to furosemide (e.g. with shock).

Nervous System Disorders

Rare: Paraesthesia may develop. Hepatic encephalopathy in patients with hepatocellular insufficiency may occur. Rare complications may include minor psychiatric disturbances.

Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension) may occur.

Vascular Disorders

Common: An increased tendency for thrombosis may also occur.

Rare: In conjunction with increased fluid excretion, there may be a reduction in blood pressure, hypotension. This may cause some impairment of powers of concentration and reaction, sensations of pressure in the head, headache, dizziness, sleepiness, feelings of weakness, disorders of vision, dryness of the mouth as well as disorders of orthostatic hypotension.
Vasculitis

General Disorders

Rare: Fever may occur.

Blood & The Lymphatic System Disorders

Uncommon: Thrombocytopenia may occur

Rare: Eosinophilia, haemoconcentration and leucopenia may develop

Very rare: Haemolytic anaemia, aplastic anaemia, agranulocytosis

Congenital & familial/genetic disorders

Increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life.

Investigations:

Disturbance of liver function tests.

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 HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss. Treatment of overdosage should be aimed at reversing dehydration and correcting electrolyte imbalance, particularly hyperkalaemia. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive. If hyperkalaemia is seen, appropriate measures to reduce serum potassium must be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Amiloride

Pharmacotherapeutic group: potassium sparing agent, ATC code: C03DB01

Furosemide

Pharmacotherapeutic group: high ceiling diuretic, ATC code: C03CA01

Mechanism of action

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

Amiloride is a mild diuretic which moderately increases the excretion of sodium and chloride, reduces potassium excretion and does not appear to act by inhibition of aldosterone.

It does not inhibit carbonic anhydrase. Amiloride adds to the natriuretic effect but diminishes the kaliuretic effect of other diuretics.

A combination of furosemide and amiloride gives a diuretic which is intended to reduce the potassium loss associated with furosemide alone and avoids the possible gastro-intestinal disturbances of potassium supplements.

5.2 Pharmacokinetic properties

Furosemide is a potent diuretic with a rapid action. Its effects are evident within 30 minutes to 1 hour after a dose by mouth, peak at 1 to 2 hours, and last for about 4 to 6 hours; after intravenous injection its effects are evident in about 5 minutes and last for about 2 hours.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize Starch
Sunset Yellow (E 110)
Pregelatinised starch
Croscarmellose sodium
Magnesium stearate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

250 µm opaque UPVC/20 µm hard temper aluminium foil or 60 gsm PVdC on 250 µm PVC/20 µm hard temper aluminium foil blister strip packs of 14 tablets in cartons of 28 and 56 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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