Data Sheet

Frumil®

NAME OF MEDICINE

Frusemide (furosemide) 40 mg and Amiloride hydrochloride 5 mg (anhydrous).

PRESENTATION

Orange tablets with break-line; FRUMIL on reverse side.

PHARMACOLOGY

Frumil is a potassium sparing diuretic which combines the potent natriuretic effect of frusemide with the potassium-conserving property of amiloride hydrochloride. The administration of high ceiling diuretics such as frusemide can result in a significant increase in potassium excretion, which may lead to hypokalaemia or metabolic alkalosis. When combined with amiloride, the amount of potassium excreted is decreased and the need for potassium supplements is eliminated. Moreover, the diuresis produced by frusemide is enhanced with amiloride if given in combination.

Frusemide acts primarily to inhibit electrolyte reabsorption in the ascending limb of the Loop of Henle; this action has also been observed in the proximal tubule.

Excretion of sodium, potassium and chloride ions is increased and water excretion enhanced. Diuresis is observed within 1 hour of administration and lasts 4-6 hours. Amiloride hydrochloride acts in the distal convoluted tubule to inhibit the exchange of sodium and potassium ions and therefore to mildly increase the natriuretic effect whilst conserving potassium.

Chloride excretion is little affected by amiloride. Diuresis occurs within 2 hours of administration of amiloride, with peak effect at 6-10 hours; the action lasts for 24 hours.

Clinical studies have indicated that Frumil consistently maintains plasma potassium levels within the normal range. The diuretic and natriuretic activity of Frumil is greater and more prolonged than frusemide alone. Diuresis was observed within 2 hours and lasted for 24 hours.

INDICATIONS

Frumil is indicated for the treatment of cardiac failure, in patients who require diuretics plus potassium supplements, or potassium sparing diuretics.

CONTRAINDICATIONS

Patients with hyperkalemia (serum potassium above 5.5 mmol per litre).

Patients with severe hypokalaemia. However, if hypokalaemia develops during treatment it can usually be corrected without interrupting administration of Frumil.

Patients with hypovolaemia or dehydration.

Patients with impaired renal function and a creatinine clearance below 30 mL/min per 1.73 m^2 body surface area, acute renal failure or anuria.

Patients with severe hyponatraemia.

Patients with pre-comatose and comatose states associated with hepatic encephalopathy.

Patients on concomitant potassium supplements.

Patients who are pregnant or breastfeeding.

Patients with a hypersensitivity to frusemide, amiloride, sulfonamides or sulfonamide derivatives, or any of the excipients of Frumil. Patients allergic to sulfonamides (eg. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to frusemide

WARNINGS

Hyperkalaemia has been observed in patients receiving amiloride hydrochloride. Frusemide can cause latent diabetes to become manifest or the insulin requirements of diabetic patients to increase. Patients with prostatic hypertrophy or impairment of micturition are at increased risk of

developing acute urinary retention. Serum uric acid levels may rise during treatment with Frumil and an acute attack of gout may be precipitated.

Cephaloridine nephrotoxicity may be increased by concomitant administration of patient diuretics such as Frumil.

PRECAUTIONS

Urinary outflow must be secured. In patients with a partial obstruction of urinary outflow (eg. 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.

Treatment with Frumil necessitates regular medical supervision. Particularly careful monitoring is required in patients with: hypotension, in patients who would be at particular risk from a pronounced fall in blood pressure (eg. significant stenoses of the coronary arteries or of the blood vessels supplying the brain), latent or manifest diabetes mellitus, gout, hepatorenal syndrome (i.e. functional renal failure associated with severe liver disease), hypoproteinaemia (eg. associated with nephrotic syndrome).

All potassium conserving diuretic combinations can cause an abnormal elevation of serum potassium. It is recommended that measurements of potassium are made at appropriate intervals and at time of dosage adjustment, particularly in elderly or diabetic patients and also in patients with confirmed or suspected renal impairment and a creatinine clearance below 60 mL/min per 1.73 m^2 body surface area as well as in cases where Frumil is taken in combination with certain other drugs which may lead to an increase in potassium concentration. Warning signs of hyperkalemia include parasthesia, muscular weakness, fatigue, flaccid paralysis extremities, bradycardia, shock, serum potassium and ECG abnormalities. Should hyperkalemia occur,

Frumil should be discontinued and measures to reduce plasma potassium may be necessary.

Regular monitoring of serum sodium, potassium and creatinine and blood glucose is generally recommended during Frumil 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). 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.

Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Frumil.

The dosage of concurrently administered cardiac glycosides or antihypertensive agents may require adjustment.

Frumil should be discontinued before a glucose tolerance test.

Caution should be exercised and the risks and benefits of combining risperidone with Lasix or other potent diuretics should be considered prior to the decision to treat. In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3% ; mean age 89 years, range 75 to 97) compared to treatment with risperidone alone (3.1% ; mean age 84 years, range 70 to 96) or frusemide alone (4.1% ; mean age 80 years, range 67 to 90). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low doses) was not associated with similar mortality findings. No pathophysiological mechanism has been identified to explain this finding and no consistent pattern for cause of death was observed. Nevertheless, caution is advised. Irrespective of treatment, dehydration was an overall risk factor for mortality and should, therefore, be carefully avoided in elderly patients with dementia.

Use in Pregnancy

Frumil must not be taken during Pregnancy.

Use in Lactation

The safety of Frumil in lactation has not been established; however, frusemide passes into breast milk and may partially inhibit lactation. The use of Frumil in lactating mothers should be avoided.

Use in Children

No experience is available regarding the use of Frumil in children.

Effects on Ability to Drive and Use Machines

Some adverse effects (eg. a pronounced fall in blood pressure) may impair the patient's ability to concentrate and react, and therefore, constitute a risk in situations where these abilities are of special importance eg. operating a vehicle or machinery.

INTERACTIONS

Combinations that are not recommended

In isolated cases intravenous administration of frusemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of Frumil concomitantly with chloral hydrate is, therefore, not recommended.

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

Precautions for use

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

Oral frusemide and sucralfate must not be taken within two hours of each other because sucralfate decreases the absorption of frusemide from the intestine and hence, reduces its effect.

Frusemide decreases the excretion of lithium salts and may cause increased serum lithium levels, resulting in increased risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored in patients receiving this combination.

Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including cases of renal failure, especially when an angiotensin converting enzyme inhibitor (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 frusemide temporarily or at least reducing the dose of frusemide for 3 days before starting treatment with or increasing the dose of an ACE inhibitor or angiotensin II receptor antagonist.

Caution should be exercised and the risks and benefits of treating a patient on risperidone with Lasix or other potent diuretics should be considered prior to the decision to use. See PRECAUTIONS regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

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.

Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the effect of Frumil. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by frusemide.

Attenuation of the effects of Frumil may occur following concurrent administration of phenytoin.

Carbenoxolone, corticosteroids, prolonged use of laxatives or ingestion of liquorice in large amounts may increase the risk of developing hypokalaemia.

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

If antihypertensive agents, diuretics or other drugs with blood-pressure lowering potential are given concomitantly with Frumil, a more pronounced fall in blood pressure must be anticipated.

Methotrexate, probenecid and other drugs which, like frusemide, undergo significant renal tubular secretion may reduce the effects of frusemide. Conversely frusemide may decrease renal elimination of these drugs. In the case of high dose treatment (in particular of both frusemide and the other drugs), this may lead to an increased risk of adverse effects due to frusemide or the concomitant medication.

The effect of anti-diabetics drugs and blood pressure-increasing sympathomimetics (eg. adrenaline, noradrenaline) may be reduced. The effects of curare-type muscle relaxants or of theophylline may be increased.

The harmful effects of nephrotoxic drugs on the kidney may be increased by frusemide.

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

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

Patients who were at high risk for radiocontrast nephropathy treated with frusemide 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.

ADVERSE EFFECTS

Metabolism and nutrition disorders

Increased excretion of sodium and chloride and consequently water. Increased excretion of other electrolytes (in particular calcium and magnesium). The two active ingredients exert opposing influences on potassium excretion. The serum potassium concentration may decrease, especially at the commencement of treatment, although, particularly as treatment is continued, the potassium concentration may increase (owing to the later onset of action of amiloride) especially in patients with impairment of renal function.

Symptomatic electrolyte disturbances, metabolic alkalosis due to frusemide, metabolic acidosis due to amiloride, dehydration and hypovolaemia especially in elderly patients, transitory increases in blood creatinine and urea levels, increase in cholesterol and triglyceride serum levels, increase in uric acid serum levels and attacks of gout. Decrease of glucose tolerance. Latent diabetes mellitus may become manifest (see Warnings and Precautions sections)

Vascular disorders

Hypotension including orthostatic hypotension, tendency for thromboses, vascultis.

Renal and urinary disorders

Acute retention of urine in patients with a partial obstruction of urinary outflow, interstitial nephritis, nephrocalcinosis/nephrolithiasis in premature infants.

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, acute pancreatitis.

Hepato-bilary disorders

Intrahepatic cholestasis, increase in liver transaminases.

Ear and labyrinth disorders

Hearing disorders and tinnitus, although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome).

Skin and subcutaneous tissue disorders

Itching, urticaria, other rashes or bulbous lesions, erythema multiforme, bulbous pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, purpura, photosensitivity. AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug

rash with eosinophilia and systemic symptoms) has been reported with the use of products containing frusemide.

Immune system disorders

Severe anaphylactic or anaphylactoid reactions (e.g. with shock).

Nervous system disorders

Paraesthesiae, hepatic encephalopathy in patients with hepatocellular insufficiency.

Blood and the lymphatic system disorders

Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia or haemolytic anaemia, eosinophilia, haemoconcentration.

General disorders and administration site conditions

Fever

DOSAGE AND ADMINISTRATION

The initial adult dose is one tablet (40 mg frusemide and 5 mg amiloride hydrochloride) to be taken each morning. This may be increased to two tablets each morning if the initial response is unsatisfactory. The total daily dose of amiloride should not exceed 20 mg.

OVERDOSAGE

Signs and Symptoms

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss eg. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias (including A-V block and ventricular fibrillation). Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment

Treatment of over-dosage should be aimed at reversing the dehydration and correcting electrolyte imbalance, particularly hyperkalaemia. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures. Attempts should be made to limit further systemic absorption of the active ingredient. Treatment is symptomatic and supportive. If hyperkalaemia is seen, appropriate measures to reduce it must be instituted.

PHARMACEUTICAL PRECAUTIONS

Special Precautions for Storage

Store below 25°C.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Calendar packs of 28 tablets (2 x 14 blisters)

FURTHER INFORMATION

Excipients

Each tablet also contains lactose, maize starch, microcrystalline cellulose, sodium starch glycollate, silicon dioxide, purified talc, magnesium stearate, sunset yellow FCF.

NAME AND ADDRESS OF SPONSOR

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