Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Frumil 40mg/5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Orange, circular, uncoated tablets, 8 mm in diameter, with a breakline on one face and 'FRUMIL' 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

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.

Recommended Dosage:
Adults: The usual adult dose is 1 tablet (40mg 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.

Elderly patients: The dosage should be adjusted according to diuretic response. Extreme care should be taken with dosage in the elderly as this patient group are more susceptible to serious side effects associated with electrolyte disturbances.

4.3 Contraindications

1. Use in patients with Addison's disease.
2. Use in patients hypersensitive to the active ingredients, furosemide, amiloride, sulfonamides or sulfonamide derivatives, or any of the excipients of Frumil. Patients allergic to sulfonamides may show cross-sensitivity to furosemide.
3. During pregnancy
4. In breast-feeding women.
5. Use in children.
6. Use in patients with impaired renal function and a creatine clearance below 30 ml/min per 1.73 m^2 body surface area, acute renal failure or anuria.
7. Use in patients with hyperkalemia
8. Use in patients with severe hypokalemia, however if hypokalemia developes during treatment it can usually be corrected without interrupting treatment.
9. Use in patients with hypovolemia or dehydration.
10. In patients with severe hyponatraemia
11. In patients with pre-comatose and comatose states associated with hepatic encephalopathy.

4.4 Special warnings and precautions for use

1. Patients who are being treated with this preparation require regular supervision with monitoring of fluid and electrolyte state to avoid excessive loss of fluid. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected.
2. The preparation should only be used with particular caution in elderly patients, or those with disorders rendering their 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.
3. 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.

4. Patients with rare hereditary problems of glucose intolerance, the Lapp lactase defiency or glucose-galactose malabsorbtion should not take this medicine.
5. Hyperuricaemia and gout may be induced by furosemide.
6. Ototoxicity may occur if given concomitantly with ototoxic drugs (see Section 4.5).
7. Bone marrow depression occasionally complicates treatment necessitating withdrawal of the product. The haemopoietic state should therefore be regularly monitored during treatment.
8. Hyponatraemia, hypochloraemia and raised blood urea nitrogen may occur during vigorous diuresis, especially in seriously ill patients. Careful monitoring of serum electrolytes, creatinine and urea should therefore be undertaken in these patients.
9. Hyperkalaemia has been observed in patients receiving amiloride hydrochloride.
10. 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 m^2 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 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). Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Frumil. 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.

The possibility exists of exacerbation or activation of systemic lupus erythematosus hence caution should be taken when administering furosemide to patients with a history of SLE.

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.

This medicinal product contains less than 1mmol sodium (23mg) per tablet, that is to say essentially "sodium free"

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 Frumil 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 Frumil.

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.

Frumil 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.

Frumil 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 Frumil. 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 Frumil

If other antihypertensives, diuretics, or drugs which can lead to a reduction in blood pressure are taken concurrently with Frumil, 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 hyperuricaemia 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).

Aliskiren reduces 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

Frumil must not be taken during pregnancy. Breast feeding 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 patients 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 following CIOMS V convention is used: (very common (>1/10), common (1/10 – 1/100), uncommon (1/100 – 1/1000), rare (1/1000 – 1/10000), very rare (<1/10000), Not known.

Blood and the lymphatic system disorders:
Rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia or haemolytic anaemia, eosinophilia, haemoconcentration.

Immune system disorders:
Rare: severe anaphylactic or anaphylactoid reaction, (e.g with shock)
Not known: exacerbation or activation of systemic lupus erythematosus

Metabolism and nutrition disorders (see section 4.4):
The two active ingredients exert opposing influences on potassium excretion. The serum potassium concentration may decrease, especially at the commencement of treatment (owing to the earlier onset of action of furosemide), 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.

Common: hypokalaemia, gout attack.

Rare: hyponatremia, urine volume increased, hyperkalemia (especially in patients with impairment of renal function), blood creatinine increased, blood cholesterol increased, blood triglycerides increased, blood uric acid increased, electrolyte disturbances (including symptomatic), metabolic alkalosis due to furosemide, dehydration/hypovolemia (especially in elderly patients), hypochloremia, hypocalcemia, hypomagnesemia, blood urea increased, glucose tolerance impaired (latent diabetes mellitus may become manifest-see section 4.5), Pseudo-Bartter syndrome.
Not known: metabolic acidosis due to amiloride

Nervous system disorders:
Rare: paraesthesia, hepatic encephalopathy in patients with hepatocellular insufficiency (see section 4,3).
Not Known: Dizziness, fainting or loss of consciousness, headache**.**

Ear and labyrinth disorders:
Rare: hearing disorders (usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephrotic syndrome) and/or when intravenous furosemide has been given too rapidly, tinnitus, deafness.
Uncommon: **deafness (sometimes irreversible)**

Vascular disorders:
Common: thrombosis.
Rare: hypotension including orthostatic hypotension (see section 4.4), vasculitis.

Gastrointestinal disorders:
Very common: nausea.
Uncommon: vomiting, diarrhoea.
Rare: pancreatitis acute.

Hepato-biliary disorders:
Rare: cholestasis, transaminases increased.

Skin and subcutaneous tissue disorders:
Common: rash.
Rare: pruritus, urticaria, dermatitis bullous, erythema multiforme, pemphigoid, dermatitis exfloliative, purpura, photosensitivity reaction. Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, DRESS (drug rash with eosinophilia and systemic symptoms).
Not Known: **acute generalised exanthematous pustulosis (AGEP)**, rashes, lichenoid reactions.

Renal and urinary disorders:
Common: urine retention (in patients with a partial obstruction of urinary outflow see section 4.4.
Rare: tubulointerstitial nephritis, nephrocalcinosis, nephrolithiasis (in premature infants).
Not Known: Urine volume increased, urine sodium increased, urine chloride increase, renal failure (see section 4.5)

General disorders and administration site conditions:
Rare: fever.

Musculoskeletal and connective tissue disorders
Not known: cases of rhabdomyolysis have been reported, often in the context of severe hypokalaemia (see section 4.3)

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 HPRA Pharmacovigilance, Website: www.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. Gastric lavage may be performed. Treatment is symptomatic and supportive. If hyperkalaemia is seen, appropriate measures to reduce potassium must be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycollate – Type A
Starch maize
Anstead sunset yellow dye (E110)
Talc
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original package in order to protect from light (Blisters)
Keep the container tightly closed (tablet container).

6.5 Nature and contents of container

● Grey HDPE tablet containers with white LDPE tamper evident cap or child resistant cap. Pack sizes: 50,100 or 500 tablets.

● White opaque PVC/Aluminium strips containing 28 tablets (14 tablets per blister strip) or 56 tablets (14 tablets per blister strip) and sample packs of 4, 7, 14 and 21 tablets.

Not all pack sizes may be marketed

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

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/101/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th January 1991

Date of last renewal: 29th January 2006

10 DATE OF REVISION OF THE TEXT

March 2024