For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only

AMIFRU 40

1. **Generic Name:**

   Amiloride and Furosemide Tablets I.P.

2. **Qualitative and quantitative composition:**

   Each uncoated tablet contains:

   Furosemide

   I.P……...40mg

   Amiloride Hydrochloride Dihydrate I.P.

   Equivalent to Anhydrous Amiloride Hydrochloride…...5

   mg Colour: Sunset yellow FCF

   The excipients used are Starch, Lactose, Sunset Yellow, Talc and Magnesium Stearate.

3. **Dosage form and strength**:

   Dosage form: Uncoated tablets

   Strength: Furosemide 40 mg and Amiloride Hydrochloride 5 mg.

4. **Clinical particulars:**

4.1 Therapeutic indication:

Amiloride and Furosemide Tablets is indicated in the treatment of oedematous states particularly in conditions where potassium ion conservation is important e.g.: Congestive cardiac failure, nephrosis, corticosteroid therapy, and ascites associated with cirrhosis.

Amiloride and Furosemide Tablets is also indicated in the treatment of mild and moderate degrees of essential hypertension.

4.2 Posology and method of administration:

Posology

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 the diuretic response; serum electrolytes and urea should be carefully monitored.

4.3 Contraindications:

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 m2 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.

Amiloride and Furosemide Tablets is contraindicated in children and adolescents under 18 years of age as safety in this age group has not yet been established.

Hypersensitivity to furosemide, amiloride, sulphonamides or sulphonamide derivatives, or any of the excipients of the product.

4.4 Special warnings and precautions for use:

Amiloride and Furosemide Tablets should be discontinued before a glucose tolerance test. Amiloride and Furosemide 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 Amiloride and Furosemide Tablets.

Frequent checks of the serum potassium level are necessary in patients with impaired renal function and a creatinine clearance below 60ml/min per 1.73m2 body surface area as well as in cases where Amiloride and Furosemide Tablets 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.

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

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

4.5 Drug-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 Amiloride and Furosemide Tablets. 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 Amiloride and Furosemide Tablets 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 Amiloride and Furosemide Tablets 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 Amiloride and Furosemide Tablets, 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. 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 Amiloride and Furosemide Tablets and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylic toxicity may be increased by furosemide. Amiloride and Furosemide Tablets 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 Amiloride and Furosemide Tablets 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 Amiloride and Furosemide Tablets 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, B2 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 Amiloride and Furosemide Tablets. 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.

4.6 Use in special populations

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.

Lactation

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 Amiloride and Furosemide Tablets.

4.7 Effects on ability to drive and use machines:

You may feel dizzy or unwell after taking Amiloride and Furosemide tablets. If this happens, do not drive or use any tools or machines.

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).

Amiloride and Furosemide 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. 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 treatment. Pancreatitis acute

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

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 Mechanism of Action:

Furosemide:

Furosemide is a 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 natiuretic but diminishes the kaliuretic effect 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 Pharmacodynamic properties:

Furosemide:

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.

The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium, chloride from the nephron is reduced hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the

glomerulus to serum proteins.

Amiloride:

Amiloride is a pyrazinoylguanidine derivative which acts as a potassium-sparing diuretic. Amiloride interferes with transport of electrolytes in the nephron. As electrogenic sodium transport is interupted the electrical potential across the tubular epithelium falls. The reduction or elimination of this potential, which is one of the driving forces for secretion of potassium, is probably the basis of the potassium-sparing effect.

5.3 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 about 3 - 4 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 Furosemide and Amiloride 40mg/5mg 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

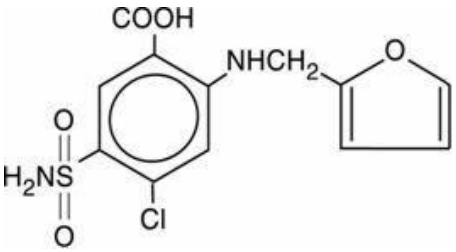
6. Nonclinical properties:

No further information available.

7. Description:

Furosemide

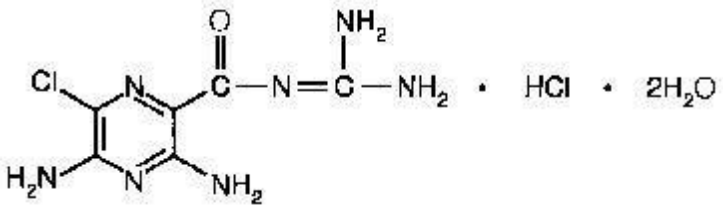
Furosemide/Frusemide is a diuretic, which is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. Furosemide is a white to off-white odorless



crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids. The structural formula is as follows:

Amiloride Hydrochloride

Amiloride HCl, an antikaliuretic-diuretic agent, is a pyrazine-carbonyl-guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. It is the salt of a moderately strong base (pKa 8.7). It is designated chemically as 3, 5-diamino-6-chloro-N-(diaminomethylene) pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular eight of 302.12. Its empirical formula is $C_6H_8ClN_7O \bullet HCl \bullet 2H_2O$ and its structural formula is:



Amiloride and Furosemide Tablets are light orange coloured, round, flat, uncoated tablets with break line on one side and plain on other side. The excipients used are Starch, Lactose, Sunset Yellow, Talc and Magnesium Stearate.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

AMIFRU-40 is available as 10x3x10 Tablets.

8.4 Storage and handing instructions:

Store in cool and dry place. Protect from light.

Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

AMIFRU 40

Amiloride and Furosemide Tablets I.P

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What AMIFRU 40 is and what it is used for

AMIFRU 40 Tablets contain two different medicines called: furosemide and amiloride hydrochloride. Both belong to a group of medicines called diuretics (water tablets). **AMIFRU 40 Tablets** can be used to stop the build-up of extra water in your body. This extra water can cause swollen ankles, shortness of breath and feeling more tired than usual.

9.2. What you need to know before you take AMIFRU 40

Do not take AMIFRU 40 Tablets if:

- You are allergic (hypersensitive) to furosemide, amiloride hydrochloride or any of the other ingredients of this medicine.
- Signs of an allergic reaction include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You are allergic to sulphonamides such as sulfadiazine or co-trimoxazole.
- You have severe problems with your kidneys.
- You have severe liver problems.
- Your doctor has told you that you have a low blood volume or are dehydrated.
- You are not passing any water (urine).
- You have too much or too little potassium or sodium in your blood (shown in blood tests).
- You have an illness called 'Addison's Disease'. This can make you feel tired and weak.
- You are breast-feeding (see "Pregnancy and breast-feeding" section below).
- You are taking other medicines which change the amount of potassium in your blood (see "Taking other medicines" section below)
- If the person taking the medicine is under 18 years. AMIFRU 40 Tablets are not suitable for children.

- Do not take AMIFRU 40 Tablets if any of the above apply to you.
- If you are not sure, talk to your doctor or pharmacist before taking AMIFRU 40 Tablets.

Warnings and precautions

Talk to your doctor or pharmacist before taking AMIFRU 40 Tablets if:

- You have difficulty in passing water (urine).
- You are 65 years of age or older.
- You have liver or kidney problems.
- You are an elderly patient with dementia and are also taking risperidone.
- You have diabetes.
- You have low blood pressure or feel dizzy when you stand up.
- You have prostate problems.
- You have gout.
- You feel dizzy or dehydrated. This can happen if you have lost a lot of water through being sick, having diarrhoea or passing water very often. It can also happen if you are having trouble drinking or eating.
- You are going to have a glucose test.
- You are taking any other water tablets.
- You have systemic lupus erythematosus.

- You are elderly, or you are on other medications, which can cause the drop of the blood pressure, and you have other medical conditions that are risks for the drop of blood pressure.
- If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking AMIFRU 40 Tablets.

Other medicines and AMIFRU 40 Tablets

Please tell your doctor or pharmacist if you are taking or have recently taken, or might take any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because AMIFRU 40 Tablets can affect the way some other medicines work. In addition, some medicines can affect the way AMIFRU 40 Tablets work.

Do not take this medicine, and tell your doctor, if you are taking:

Medicines, which change the amount of potassium in your blood. These include potassium supplements such as potassium chloride or certain water tablets (diuretics) such as triamterene.

The following medicines can affect the way AMIFRU 40 Tablets work and increase the chance of you getting side effects:

- Medicines such as ramipril, enalapril, perindopril (called 'ACE inhibitors') or losartan, candesartan, irbesartan (called 'angiotensin II receptor antagonists'). Your doctor may need to change the dose of your tablets or ask you to stop taking them.
- Medicines for high blood pressure or heart problems. Your doctor may need to change the dose of your medicine.
- Medicines used as a general anaesthetic for relaxing your muscles during surgery.
- Medicines for diabetes. These may not work as well when you are taking AMIFRU 40 Tablets.
- Theophylline - used for wheezing or difficulty in breathing.

- Phenytoin - used for epilepsy. This can lower the effect of AMIFRU 40 Tablets.

The following medicines can increase the chance of side effects when taken with AMIFRU 40 Tablets:

- Lithium - used for mental illnesses. To help stop side effects your doctor may need to change the dose of your lithium and check the amount of lithium in your blood.
- Cisplatin - used for some cancers.
- Digoxin - used for heart problems. Your doctor may need to change the dose of your medicine.
- Non-steroidal anti-inflammatory drugs (NSAIDS) - used for pain and inflammation such as aspirin, ibuprofen, ketoprofen or indomethacin.
- Carbamazepine - used for epilepsy.
- Aminoglutethimide - used for breast cancer.
- Ciclosporin - used to stop the rejection of organs after a transplant.
- Methotrexate - used for cancers of the skin, joint or bowel diseases.
- Carbenoxolone - used for ulcers of the foodpipe (gullet).
- Reboxetine - used for depression.
- Amphotericin - used for fungal infections if used for a long time.
- Corticosteroids - used for inflammation such as prednisolone.
- Liquorice - often used in cough medicines if taken in large amounts.
- Probenecid (used with another HIV medicine).
- Medicines for infection such as gentamicin, amikacin, neomycin, netilmicin, tobramycin, vancomycin or high doses of cephalosporins.
- Medicines used as injections before X-ray examinations.
- Medicines used for constipation (laxatives) if used for a long time such as bisacodyl or senna.
- Medicines for asthma when given in high doses such as salbutamol, terbutaline sulphate, salmeterol, formoterol or bambuterol.
- Other water tablets (diuretics) such as bendroflumethiazide. Your doctor may need to change the dose of your medicine.

Pregnancy and breast-feeding

- Do not take AMIFRU 40 Tablets if you are pregnant.

Talk to your doctor before taking this medicine if you are pregnant, might become pregnant, or think you might be pregnant.

- Do not breast-feed if you are taking AMIFRU 40 Tablets.
- This is because small amounts may pass into the mother's milk. Talk to your doctor before taking this medicine if you are breast-feeding or planning to breast-feed. Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines

- You may feel dizzy or unwell after taking AMIFRU 40 Tablets. If this happens, do not drive or use any tools or machines.

AMIFRU 40 Tablets contain Sunset Yellow and Lactose.

This medicine contains:

- A colour called 'sunset yellow' (E110). This may cause allergic reactions.
- Lactose. If you have been told by your doctor that you cannot tolerate some sugars, talk to your doctor before taking this medicine.

9.3. How to take AMIFRU 40

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Taking this medicine

- Take this medicine by mouth.
- Swallow the tablets whole with a drink of water.
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor.

How much AMIFRU 40 Tablets to take

The usual dose is one or two tablets first thing in the morning. Your doctor will tell you how many tablets to take.

If you are taking sucralfate (a medicine for stomach ulcers)

Do not take sucralfate at the same time as AMIFRU 40 Tablets. Take your dose at least 2 hours before or after AMIFRU 40 Tablets. This is because it can affect the way your medicine works.

If you take more AMIFRU 40 Tablets than you should

If you think, you may have taken more AMIFRU 40 Tablets than you should, or if a child has swallowed any of your tablets, tell your doctor or got to your nearest hospital casualty department straight away. Remember to take with you any medicine that is left so the doctor knows what you have taken. The following effects may happen: dry mouth, feeling thirsty, muscle pain or cramps, feeling sick or being sick (vomiting), weak or uneven heartbeat, feeling dizzy, weak or sleepy.

If you forget to take AMIFRU 40 Tablets

If you forget a dose, take it as soon as you remember it. Then continue the following morning as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking AMIFRU 40 Tablets

Keep taking AMIFRU 40 Tablets until your doctor tells you to stop taking it.

Blood tests

Your doctor may carry out blood tests to check that the levels of some salts in the blood are at the correct levels.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment.

Frequency not known (cannot be estimated from the available data)

- If you have an allergic reaction. The signs may include inflammation of the kidney (nephritis),
- Swollen ankles or high blood pressure, skin rashes, change in skin colour, severe blistering of the skin, being more sensitive to the sun than usual, high temperature (fever), and itching
- Severe allergic reactions. The signs may include shock such as difficulty in breathing, cold clammy skin, pale skin colour and racing heartbeat.
- Severe stomach or back pain. These could be signs of ‘pancreatitis.
- Bruising more easily, getting more infections, feeling weak or tired more than usual.
- AMIFRU 40 Tablets can affect the number of blood cells, causing serious blood problems.
- Increased thirst, headache, feeling dizzy or light-headed, fainting, confusion, muscle or joint pains or weakness, cramps or spasms, stomach upsets or uneven heartbeats. These could be signs of dehydration or changes in your normal body chemicals. Severe dehydration can also lead to blood clots or ‘gout’.
- You notice yellowing of your skin or eyes and your urine becomes darker in colour.
- These could be signs of a liver problem. In patients who already have liver problems, a more

serious liver problem known as liver encephalopathy may occur. Symptoms include forgetfulness, fits, mood changes and coma.
- Blistering or peeling of the skin around the lips, eyes, mouth, nose and genitals, flu-like
- Symptoms and fever. This could be a condition called Stevens-Johnson syndrome. In a more severe form of the condition called Toxic.
- Epidermal Necrolysis, layers of the skin may peel off to leave large areas of raw exposed skin all over the body.
- Acute generalised exanthematous pustulosis (AGEP) (acute febrile drug eruption), symptoms include the skin becoming red with swollen areas covered in numerous small pustules.
- Dizziness, fainting and loss of consciousness.

Tell a doctor as soon as possible if you have any of the following side effects:

- **Uncommon (may affect up to 1 in 100 people)**
  - ❖ Deafness (sometimes irreversible)
- **Frequency not known (cannot be estimated from the available data)**
  - ❖ Problems hearing or ringing in the ears (tinnitus). This especially affects people who already have problems with their kidneys
  - ❖ Tingling or feeling numb on the skin
  - ❖ Small changes in your mood such as feeling agitated or anxious.
  - ❖ Headaches, feeling dizzy or light-headed when standing up quickly. Also loss of concentration,
  - ❖ Slower reactions, feeling sleepy or weak, problems with your sight, dry mouth. This could be due to low blood pressure

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice, any side effects not listed in this leaflet.

- **Frequency not known (cannot be estimated from the available data)**
  - ❖ Feeling sick (nausea) or a general feeling of being unwell, diarrhoea and being sick (vomiting) and constipation.
  - ❖ People with bladder and prostate problems may notice pain when passing water.
  - ❖ This is due to an increase in the amount of water passed.
- If you have diabetes you may be less able to control the levels of glucose in your blood
- Passing more water (urine) than you usually do. This normally happens 1 or 2 hours after taking this medicine.
- Symptoms vary considerably between patients but the most common are: joint aches and pains, swollen joints, headaches, increased sensitivity to sunlight, skin rashes, kidney problems, fatigue and weakness, mouth ulcers, hair loss, anxiety and depression, fevers and night sweats, abdominal pain, chest pain, shortness of breath, anaemia (Systemic lupus erythematosus).
- Lichenoid reactions, characterized as small, itchy reddish-purple, polygon-shaped lesions on the skin, genitals or in the mouth.

Blood tests

- AMIFRU 40 Tablets can change the levels of liver enzymes or body fats known as cholesterol and triglycerides shown up on blood tests.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5. How to store AMIFRU 40

- Keep this medicine out of the sight and reach of children.
- Do not take AMIFRU 40 Tablets after the expiry date, which is stated on the carton and blister pack after EXP. The expiry date refers to the last day of that month.
- Store in a cool and dry place. Keep the blister strip in the outer carton in order to protect from light and moisture.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6. Contents of the pack and other information

What AMIFRU 40 contains

One of the active substance is furosemide 40 mg. This is the new name for frusemide 40 mg. The ingredient itself has not changed. The active substances are furosemide and amiloride hydrochloride. Each tablet contains 40 mg furosemide and 5 mg amiloride hydrochloride (as anhydrous).

The other ingredients are Starch, Lactose, Sunset Yellow, Talc and Magnesium Stearate.

Colour: Sunset yellow FCF.

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim – 737135

OR

Manufactured in India by:

Windlas Biotech Limited (Plant-IV)

Plot No. 183 & 192,

Mohabewala Industrial Area,

Dehradun-248110, Uttarakhand

11. Details of permission or licence number with date

Torrent Pharmaceuticals Ltd.

Mfg Lic No. M/563/2010 issued on 23.12.2016

Windlas Biotech Limited (Plant-IV)

Mfg Lic No. 47/UA/2009

12. Date of revision

APR 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/AMIFRU 40, 5 mg/APR-2022/03/PI