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

AMIFRU PLUS

1. **Generic Name:**

   TORSEMIDE AND AMILORIDE HYDROCHLORIDE TABLETS

2. **Qualitative and quantitative composition:**

   Each uncoated tablet contains:
   Torsemide I.P. ..... 10 mg
   Amiloride Hydrochloride IP
   equivalent to anhydrous
   amiloride hydrochloride ..... 5 mg
   Excipients ..... q.s.

   LACTOSE , MICROCRYSTALLINE CELLU, CROSSPOVIDONE XL-10, POLYVINYL PYRROLIDONE (K-30), CROSSPOVIDONE XL-10, MAGNESIUM STEARATE

3. **Dosage form and strength**

   Dosage form: Uncoated tablets
   Strength: Torasemide 10mg and Amiloride Hydrochloride 5 mg.

4. **Clinical particulars**

4.1 Therapeutic indication:

Treatment of oedema due to congestive heart failure; hepatic, pulmonary or renal oedema and hypertension oedema.

4.2 Posology and method of administration

One tablet twice a day orally or as suggested by physician.

Torasemide

Adults
Oedema: The usual dose is 5mg once daily. If necessary, the dose can be increased stepwise up to 20mg once daily. In individual cases, as much as 40mg torasemide/day has been administered.

Elderly
No special dosage adjustments are necessary.

Children
There is no experience of torasemide in children.

Amiloride
Adults:
Initially 5mg twice daily, adjusted according to response. The dosage may be increased up to a maximum of 20mg daily.
Used as an adjunct to other diuretics for hypertension and congestive heart failure: Initially 5mg or 10mg daily.

Cirrhosis with ascites: Initially 5mg daily.

Elderly:
The dosage should be adjusted according to renal function, blood electrolytes and diuretic response.

Children

Under 18 years:
Not indicated.

4.3 Contraindications

Torasemide

Renal failure with anuria; hepatic coma and pre-coma; hypotension; pre- existing hypovolaemia; pregnancy and lactation; hypersensitivity to torasemide and sulphonylureas; cardiac arrhythmias, simultaneous therapy with aminoglycosides or cephalosporins, or renal dysfunction due to drugs which cause renal damage.

Amiloride

Hyperkalaemia, severe renal impairment, prior sensitivity to amiloride. Other potassium-sparing drugs and potassium supplements are contraindicated during amiloride therapy. The safety of amiloride hydrochloride for use in children under 18 years of age has not been established.

4.4 Special warnings and precautions for use:

Torasemide

Hypokalaemia, hyponatraemia, hypovolaemia and disorders of micturition must be corrected before treatment.

On long-term treatment with torasemide, regular monitoring of the electrolyte balance, glucose, uric acid, creatinine and lipids in the blood, is recommended.

Careful monitoring of patients with a tendency to hyperuricaemia and gout is recommended. Carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.

As for other drugs which produce changes in blood pressure, patients taking torasemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

Difficulty with micturition

Particular caution is required in patients with difficulty with micturition including prostatic hypertrophy because they have an increased risk of developing acute urinary retention and require careful close monitoring.

Amiloride

Amiloride should be given with caution to elderly patients, patients likely to develop acidosis, patients with diabetes mellitus and those with impaired hepatic or renal function. Patients with impaired renal function should be monitored carefully for serum electrolytes and blood urea

levels, as should seriously ill patients, such as those with hepatic cirrhosis with ascites and metabolic alkalosis or those with resistant oedema who are also taking diuretics. Patients taking amiloride either alone or with other diuretics or angiotensin-converting enzyme inhibitors may develop hyperkalaemia.

Serum electrolytes and blood urea should be monitored periodically. If hyperkalaemia occurs, amiloride hydrochloride should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

Amiloride should be discontinued at least three days before a glucose tolerance test because of the risk of provoking severe hyperkalaemia.

4.5 Drug-Interaction:

Torasemide

When used simultaneously with cardiac glycosides, a potassium and/or magnesium deficiency may increase sensitivity of the cardiac muscle to such drugs. The kaliuretic effect of mineralo- and glucocorticoids and laxatives may be increased.

As with other diuretics, the effect of antihypertensive drugs given concomitantly may be potentiated.

Torasemide, especially at high doses, may potentiate the toxicity of aminoglycoside antibiotics, cisplatin preparations, the nephrotoxic effects of cephalosporins, and the cardio- and neurotoxic effect of lithium. The action of curare-containing muscle relaxants and of theophylline can be

Potentiated. In patients receiving high doses of salicylates, salicylate toxicity may be increased. The action of anti-diabetic drugs may be reduced.

Sequential or combined treatment, or starting a new co-medication with an ACE inhibitor may result in transient hypotension. This may be minimised by lowering the starting dose of the ACE inhibitor and/or reducing or stopping temporarily the dose of torasemide. Torasemide may decrease arterial responsiveness to pressor agents e.g. adrenaline, noradrenaline.

Non-steroidal anti-inflammatory drugs (eg. Indometacin) and probenecid may reduce the diuretic and hypotensive effect of torasemide.

Concomitant use of torasemide and colestyramine has not been studied in humans, but in an animal study co-administration of cholestyramine decreased absorption of oral torasemide.

Amiloride

Alcohol: Postural hypotension associated with diuretic therapy may be enhanced. Aldesleukin: Enhanced hypotensive effect may occur when aldesleukin and amiloride are used concomitantly.

Anaesthetics, general: Enhanced hypotensive effect may occur when general anaesthetics and amiloride are used concomitantly.

Analgesics: Diuretics increase the risk of nephrotoxicity with NSAIDs. Indometacin and possibly other NSAIDs increase the risk of hyperkalaemia with potassium-sparing diuretics.

Indometacin and ketorolac antagonise the diuretic effect.

Antiarrhythmics: The antiarrhythmic activity of quinidine can be opposed by amiloride. Antidepressants: increased risk of postural hypotension with tricyclics. Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs).

Antidiabetic agents: Chlorpropamide increases the risk of hyponatraemia associated with thiazides in combination with potassium sparing diuretics.

Antiepileptics: increased risk of hyponatraemia with carbamazepine.

Antihypertensives: An enhanced hypotensive effect (which can be extreme) can occur with antihypertensives, including ACE inhibitors, angiotensin-II antagonists, calcium channel blockers, beta blockers, alpha blockers (increased risk of first dose hypotension) or hydralazine. With ACE inhibitors and angiotensin-II antagonists there is also an increased risk of hyperkalaemia.

Antipsychotics: Lithium should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Enhanced hypotensive effect may occur when phenothiazines and amiloride are used concomitantly.

Corticosteroids: Fluid retention associated with corticosteroid use may antagonise the diuretic/antihypertensive response.

Dopaminergics: Enhanced hypotensive effect may occur when levodopa and amiloride are used concomitantly.

Hormones and other endocrine drugs: Combined oral contraceptives and oestrogens may antagonise the diuretic effect. There is an increased risk of hyperkalaemia with trilostane.

Immunosuppressants: increased risk of hyperkalaemia with ciclosporin and tacrolimus. Increased risk of nephrotoxicity with concomitant use of ciclosporin and amiloride.

Muscle relaxants: enhanced hypotensive effect with baclofen and tizanidine.

Nitrates: Enhanced hypotensive effect may occur when nitrates and amiloride are used concomitantly.

Potassium conserving agents, potassium supplements: When amiloride is administered concomitantly with potassium conserving agents or potassium supplements, there is an increased risk of hyperkalaemia.

Prostaglandins: Hypotensive effect may be potentiated by alprostadil.

Ulcer-healing agents: Amiloride antagonises the ulcer-healing effect of carbenoxolone.

Laboratory value alterations: Creatinine clearance: Amiloride blocks the tubular secretion of creatinine, leading to falsely high measurements of creatinine clearance.

4.6 Use in special populations

FERTILITY, PREGNANCY AND LACTATION

Torasemide

There are no data from experience in humans of the effect of torasemide on the embryo and foetus. Whilst studies in the rat have shown no teratogenic effect, malformed foetuses have been observed after high doses in pregnant rabbits. No studies have been conducted on excretion in breast milk. Consequently, torasemide is contra-indicated in pregnancy and lactation.

Amiloride

Amiloride is not recommended for use during pregnancy or lactation. The potential benefits of the drug must be weighed against possible hazards to the foetus if it is administered to a woman of child bearing age.

4.7 Effects on ability to drive and use machines:

As for other drugs which produce changes in blood pressure, patients taking this drug should be warned not to drive or operate machinery if they experience dizziness or related Symptoms.

4.8 Undesirable effects:

Torasemide

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:Very common (≥1/10) Common (≥1/100 to <1/10) Uncommon (≥1/1,000 <1/100) Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000) Not known (cannot be estimated from available data) The following undesirable effects were observed whereas the frequency of undesirable effect is not known:

Blood and lymphatic system disorders
Frequency not known: Thrombocytopenia, Leukopenia, Anaemia

Immune system disorders
Very rare: Allergic skin reactions (eg Pruritus, Exanthema), Photosensitivity reaction
Frequency not known: Serious skin reactions (eg Stevens-Johnson syndrome, Toxic epidermal necrolysis

Metabolism and nutrition disorders
Common: Metabolic alkalosis, Fluid and electrolyte imbalance (eg Hypovolaemia, Hyponatraemia)

Nervous system disorders
Common: Headache, Dizziness
Frequency not known: Cerebral ischaemia, Parenthesia, confusional state

Eye disorders
Frequency not known: Visual impairment

Ear and labyrinth disorders Frequency not known: tinnitus, Deafness

Cardiac disorders

Frequency not known: Acute myocardial infarction, Myocardial ischaemia, Angina pertoris, Syncope, Hypotension

Vascular disorders
Frequency not known: Embolism

Gastrointestinal disorders
Common: Gastrointestinal disorder (e.g. Loss of appetite, abdominal pain upper, Nausea, Vomiting, Diarrhoea, Constipation) Frequency not known: Dry mouth, Pancreatitis

Hepatobiliary disorders
Uncommon: Hepatic enzyme increased (e.g. Gamma-glutamyltransferase increased)

Skin and subcutaneous tissue disorders
Very rare: Allergic skin reactions (e.g. Pruritus, Exanthema), Photosensitivity reaction Frequency not known: Serious skin reactions (e.g. Stevens-Johnson syndrome, Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Common: Muscle spasms

Renal and urinary disorders
Uncommon: Urinary retention, Bladder dilatation Rare: Blood urea increased, Blood creatinine increased

General disorders and administration site conditions
Common: Fatigue, Asthenia

Investigations
Uncommon: Blood uric acid increased, Blood glucose increased, Lipids increased (e.g. Blood triglycerides increased, Blood cholesterol increased)

Amiloride

Amiloride is usually well tolerated. Except for hyperkalaemia significant side effects are infrequent. Reported side-effects include the following:

Blood and lymphatic system disorders: Aplastic anaemia and neutropenia have been reported rarely.

Psychiatric disorders: Decreased libido, somnolence, mental confusion, or minor psychiatric changes may occur.

Nervous system disorders: Encephalopathy, paraesthesia. Eye disorders: Visual changes.

Cardiac disorders: Angina pectoris, arrhythmias, palpitations, postural hypotension**,** dizziness. Respiratory, thoracic and mediastinal disorders: Dyspnoea, cough.

Gastrointestinal disorders: Nausea, vomiting, constipation or diarrhoea, abdominal pain.

Hepatobiliary disorders: Abnormal liver function. A deepening of jaundice has occurred in cirrhotic patients receiving amiloride hydrochloride alone, but the relationship to amiloride is uncertain.

Skin and subcutaneous tissue disorders: Alopecia, rash, pruritus.

Renal and urinary disorders: Effects on electrolyte balance e.g. hyperkalaemia (particularly in elderly patients, diabetics and patients with renal impairment) and hyponatraemia occasionally occur. Signs include dry mouth, thirst, headache, muscle cramps and weakness. Rises in blood- urea-nitrogen concentrations may occur with amiloride.
Reproductive and breast disorders: Impotence.

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:

Torasemide
Symptoms and signs
No typical picture of intoxication is known. If overdosage occurs, then there may be marked diuresis with the danger of loss of fluid and electrolytes which may lead to somnolence, confusion, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, hemoconcentration dehydration and circulatory collapse. Gastrointestinal disturbances may occur.

Treatment
No specific antidote is known. Symptoms and signs of overdosage require the reduction of the dose or withdrawal of torasemide, and simultaneous replacement of fluid and electrolytes.

Amiloride
Symptoms
The most likely signs and symptoms are dehydration and electrolyte imbalance which should be treated by established methods. Amiloride should be discontinued and the patient observed closely.

Treatment
No specific antidote is available. Patients who present within one hour of overdose may be administered activated charcoal. Treatment should be symptomatic and supportive. If hyperkalaemia occurs, active measures should be taken to reduce plasma potassium levels.

5. Pharmacological properties:

5.1 Pharmacodynamic properties

Torasemide

Pharmacotherapeutic group: High ceiling diuretics, sulphonamide monodrugs, ATC code: C03CA04

Torasemide is a loop diuretic. However, at low doses its pharmacodynamic profile resembles that of the thiazide class regarding the level and duration of diuresis. At higher doses, torasemide induces a brisk diuresis in a dose dependant manner with a high ceiling of effect.

Torasemide acts as a salidiuretic by inhibition of renal sodium and chloride reabsorption in the ascending limb of the loop of Henle. After oral administration the onset of diuresis is within the 1st hour with a peak action within 2 to 3h. The action may last up to 12h.

In healthy subjects an increase in dose results in a linear increase in urine excretion corresponding to the logarithm of the dose (high-ceiling activity) within the 5 to 100 mg dose range. An increase in diuresis may also take place if other diuretics are no longer active, eg in the presence of impaired renal function.

In renal failure endogenous organic acids compete with loop diuretics for the acid secretion mechanism in the proximal tubule. Therefore, the torasemide dose has to be adequately increased in order to achieve effective amounts of drug at the site of action.

Torasemide leads to a gentle removal of edema and especially to an improvement of the working condition of the heart failure by reducing the preload and afterload. In patients with severe to endstage chronic renal failure there is a reduction of aterial blood pressure in addition to removal of edema and maintenance of residual diuresis.

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.

5.2 Pharmacokinetic properties

Torasemide

Absorption

Torasemide is absorbed rapidly and almost completely after oral administration, and peak serum levels are reached after one to two hours.

Serum protein binding

More than 99% of torasemide is bound to plasma proteins.

Distribution

The apparent distribution volume is 16 litres.

Metabolism

Torasemide is metabolised to three metabolites, M1, M3 and M5 by stepwise oxidation, hydroxylation or ring hydroxylation. Further metabolites (M2 and M4) have been found in animal experiments, but not in humans.

Elimination

The terminal half-life of torasemide and its metabolites is three to four hours in healthy subjects. Total clearance of torasemide is 40ml/min and renal clearance about 10ml/min.

About 80% of the dose administered is excreted as torasemide and metabolites into the renal tubule - torasemide 24%, M1 12%, M3 3%, M5 41%.

In patients with congestive heart failure and disorders of liver fnction, the elimination half-lives of torasemide and metabolite M5 are only slightly increased compared with those in healthy volunteers. The amounts of torasemide and metabolites excreted in the urine are similar to those in healthy subjects; therefore, no accumulation is to be expected.

In the presence of renal failure, elimination half-life of torasemide is unchanged.

Amiloride

Amiloride is incompletely absorbed from the gastrointestinal tract (approximately 50% is absorbed).

Peak serum concentrations are achieved about three to four hours after oral administration. Amiloride does not bind to plasma proteins and has an apparent volume of distribution greater than body water. Amiloride is not metabolised.

Amiloride is secreted in the proximal tubule of the kidney and excreted in the urine unchanged. The half-life of amiloride is about 6 hours.

6. Nonclinical properties:

Torasemide

Acute toxicity Very low toxicity. Chronic toxicity

The changes observed in toxicity studies in dogs and rats at high doses are attributable to an excess pharmacodynamic action (diuresis). Changes observed were weight reduction, increases in creatinine and urea and renal alterations such as tubular dilatation and interstitial nephritis. All drug induced changes were shown to be reversible.

Teratogenicity

Reproduction toxicology studies in the rat have shown no teratogenic effect, but malformed foetuses have been observed after high doses in pregnant rabbits. No effects on fertility have been seen.

Torasemide showed no mutagenic potential. Carcinogenicity studies in rats and mice showed no tumourigenic potential.

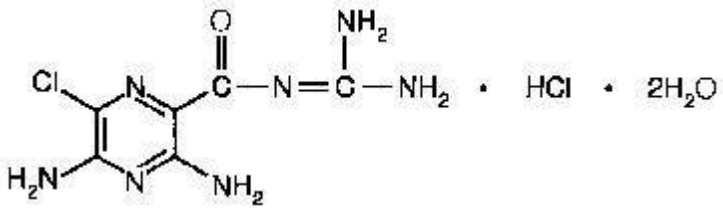
Amiloride

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

7. Description:

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 C6H8ClN7O•HCl•2H2O and its structural formula is:



Torasemide

Torsemide is 3-pyridinesulfonamide, V-[[(1-methylethyl) amino] carbonyl]-4-[(3-methylphenyl0amino]-1-Isopropyl-3 [(4-*m*-toludino-3-pyridyl) sulfonyl] urea. Torsemide contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{16}H_{20}N_4O_3S$, calculated on the anhydrous basis.

Formulation Description: White to off white, round, flat, bevelled edge, uncoated tablets with 'S5' debossing on one side and plain on other side.

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-PLUS is available as 10x5x10 Tablets.

8.4 Storage and handing instructions:

Store at temperature not exceeding 30°C, Protect from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

AMIFRU PLUS

Torasemide and Amiloride

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 PLUS is and what it is used for

AMIFRU PLUS Tablets contain two different medicines called: Torasemide and amiloride hydrochloride. Both belong to a group of medicines called diuretics (water tablets).

AMIFRU PLUS Tablets can be used Treatment of oedema due to congestive heart failure; hepatic, pulmonary or renal oedema and hypertension oedema.

9.2. What you need to know before you take AMIFRU PLUS Do not take AMIFRU PLUS

Tablets if:

- You are allergic (hypersensitive) to Torasemide, 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 PLUS Tablets are not suitable for children.
- Do not take AMIFRU PLUS Tablets if any of the above apply to you.
- If you are not sure, talk to your doctor or pharmacist before taking AMIFRU PLUS Tablets.

Warnings and precautions

Torasemide

Hypokalaemia, hyponatraemia, hypovolaemia and disorders of micturition must be corrected before treatment.

On long-term treatment with torasemide, regular monitoring of the electrolyte balance, glucose, uric acid, creatinine and lipids in the blood, is recommended.

Careful monitoring of patients with a tendency to hyperuricaemia and gout is recommended. Carbohydrate metabolism in latent or manifest diabetes mellitus should be monitored.

As for other drugs which produce changes in blood pressure, patients taking torasemide should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

Difficulty with micturition

Particular caution is required in patients with difficulty with micturition including prostatic hypertrophy because they have an increased risk of developing acute urinary retention and require careful close monitoring.

Amiloride

Amiloride should be given with caution to elderly patients, patients likely to develop acidosis, patients with diabetes mellitus and those with impaired hepatic or renal function. Patients with impaired renal function should be monitored carefully for serum electrolytes and blood urea levels, as should seriously ill patients, such as those with hepatic cirrhosis with ascites and metabolic alkalosis or those with resistant oedema who are also taking diuretics. Patients taking amiloride either alone or with other diuretics or angiotensin-converting enzyme inhibitors may develop hyperkalaemia.

Serum electrolytes and blood urea should be monitored periodically. If hyperkalaemia occurs, amiloride hydrochloride should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

Amiloride should be discontinued at least three days before a glucose tolerance test because of the risk of provoking severe hyperkalaemia.

9.3. How to take AMIFRU PLUS

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 PLUS 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 take more AMIFRU PLUS Tablets than you should

If you think, you may have taken more AMIFRU PLUS 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 PLUS 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 PLUS Tablets

Keep taking AMIFRU PLUS 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.

Torasemide

Blood and lymphatic system disorders

Frequency not known: Thrombocytopenia, Leukopenia, Anaemia

Immune system disorders

Very rare: Allergic skin reactions (eg Pruritus, Exanthema), Photosensitivity reaction
Frequency not known: Serious skin reactions (eg Stevens-Johnson syndrome, Toxic epidermal necrolysis

Metabolism and nutrition disorders

Common: Metabolic alkalosis, Fluid and electrolyte imbalance (eg Hypovolaemia, Hyponatraemia)

Nervous system disorders

Common: Headache, Dizziness

Frequency not known: Cerebral ischaemia, Parenthesia, confusional state

Eye disorders
Frequency not known: Visual impairment

Ear and labyrinth disorders Frequency not known: tinnitus, Deafness

Cardiac disorders
Frequency not known: Acute myocardial infarction, Myocardial ischaemia, Angina pertoris, Syncope, Hypotension

Vascular disorders
Frequency not known: Embolism

Gastrointestinal disorders
Common: Gastrointestinal disorder (e.g. Loss of appetite, abdominal pain upper, Nausea, Vomiting, Diarrhoea, Constipation) Frequency not known: Dry mouth, Pancreatitis

Hepatobiliary disorders
Uncommon: Hepatic enzyme increased (e.g. Gamma-glutamyltransferase increased)

Skin and subcutaneous tissue disorders
Very rare: Allergic skin reactions (e.g. Pruritus, Exanthema), Photosensitivity reaction Frequency not known: Serious skin reactions (e.g. Stevens-Johnson syndrome, Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Common: Muscle spasms

Renal and urinary disorders
Uncommon: Urinary retention, Bladder dilatation Rare: Blood urea increased, Blood creatinine increased

General disorders and administration site conditions
Common: Fatigue, Asthenia

Investigations
Uncommon: Blood uric acid increased, Blood glucose increased, Lipids increased (e.g. Blood triglycerides increased, Blood cholesterol increased)

Amiloride

Amiloride is usually well tolerated. Except for hyperkalaemia significant side effects are infrequent. Reported side-effects include the following:

Blood and lymphatic system disorders: Aplastic anaemia and neutropenia have been reported rarely.

Psychiatric disorders: Decreased libido, somnolence, mental confusion, or minor psychiatric changes may occur.

Nervous system disorders: Encephalopathy, paraesthesia. Eye disorders: Visual changes.

Cardiac disorders: Angina pectoris, arrhythmias, palpitations, postural hypotension**,** dizziness. Respiratory, thoracic and mediastinal disorders: Dyspnoea, cough.

Gastrointestinal disorders: Nausea, vomiting, constipation or diarrhoea, abdominal pain.

Hepatobiliary disorders: Abnormal liver function. A deepening of jaundice has occurred in cirrhotic patients receiving amiloride hydrochloride alone, but the relationship to amiloride is uncertain.

Skin and subcutaneous tissue disorders: Alopecia, rash, pruritus.

Renal and urinary disorders: Effects on electrolyte balance e.g. hyperkalaemia (particularly in elderly patients, diabetics and patients with renal impairment) and hyponatraemia occasionally occur. Signs include dry mouth, thirst, headache, muscle cramps and weakness. Rises in blood- urea-nitrogen concentrations may occur with amiloride.
Reproductive and breast disorders: Impotence.

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 PLUS

- Keep this medicine out of the sight and reach of children.
- Do not take AMIFRU PLUS 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 PLUS contains

The active substances are Torasemide and amiloride hydrochloride. Each tablet contains 10 mg Torasemide and 5 mg amiloride hydrochloride (as anhydrous).

The other ingredients are each uncoated tablets contains: - Torasemide IP 10mg

Amiloride hydrochloride IP equivalent to anhydrous amiloride hydrochloride 5mg

PRESENTATION

AMIFRU-PLUS is available as 10x5x10 Tablets.

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

Windlas Biotech Limited (Plant-IV)

MFG lic. M/563/2010 date-23.12.2016

12. Date of revision

APR 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/AMIFRU PLUS 5,10mg /APR-2022/02/PI