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

Amifru S Tablets

(Frusemide and Spironolactone Tablets)

COMPOSITION

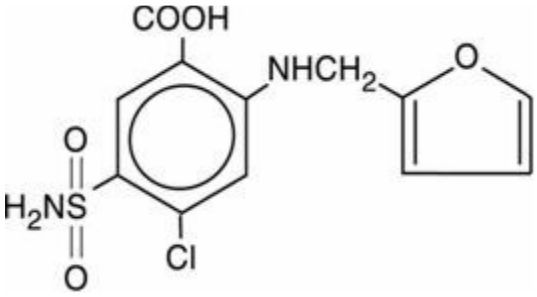
Each tablets contains
Frusemide IP 20mg
Spironolactone IP 50mg
Colors: Quinoline yellow, Brilliant blue FCF and Titanium dioxide IP.

Boxed Warning:
Furosemide
Furosemide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule must be adjusted to the individual patient's needs.
Spironolactone
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Spironolactone should be used only in those conditions described under Indication section. Unnecessary use of this drug should be avoided.

DESCRIPTION

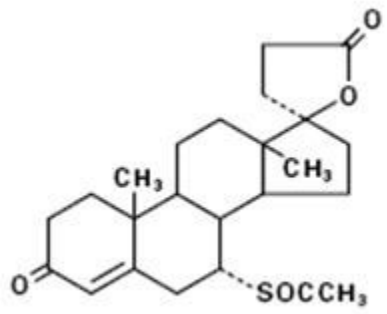
Furosemide

Furosemide 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 CAS Registry Number is 54-31-9.
The structural formula is as follows:



Spironolactone

Spironolactone - aldosterone antagonist 17-hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone acetate, which has the following structural formula:



Spironolactone is practically insoluble in water, soluble in alcohol, and freely soluble in benzene and in chloroform

CLINICAL PHARMACOLOGY

Furosemide

Pharmacodynamic

Investigations into the mode of action of furosemide have utilized micropuncture studies in rats, stop flow experiments in dogs and various clearance studies in both humans and experimental animals. It has been demonstrated that furosemide inhibits primarily the absorption of sodium and chloride not only in the proximal and distal tubules but also in the loop of Henle. The high degree of efficacy is largely due to the unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone.

Pharmacokinetics

Recent evidence suggests that furosemide glucuronide is the only or at least the major biotransformation product of furosemide in man. Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 μg/mL are 91 to 99% bound in healthy individuals. The unbound fraction averages 2.3 to 4.1% at therapeutic concentrations.

The onset of diuresis following oral administration is within 1 hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

In fasted normal men, the mean bioavailability of furosemide from furosemide tablets and furosemide oral solution is 64% and 60%, respectively, of that from an intravenous injection of the drug reported. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (87 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but times-to-peak do not differ among doses. The terminal half-life of furosemide is approximately 2 hours.

Significantly more furosemide is excreted in urine following the IV injection than after the tablet or oral solution. There are no significant differences between the two oral formulations in the amount of unchanged drug excreted in urine.

Spironolactone

Pharmacodynamic

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased

amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy.

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension, despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension.

Through its action in antagonizing the effect of aldosterone, spironolactone inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

Spironolactone has not been demonstrated to elevate serum uric acid, to precipitate gout, or to alter carbohydrate metabolism.

Pharmacokinetics

Spironolactone is rapidly and extensively metabolized. Sulfur-containing products are the predominant metabolites and are thought to be primarily responsible, together with spironolactone, for the therapeutic effects of the drug. The following pharmacokinetic data were reported from 12 healthy volunteers following the administration of 100 mg of spironolactone (spironolactone film-coated tablets) daily for 15 days. On the 15th day, spironolactone was given immediately after a low-fat breakfast and blood was drawn thereafter.

	Accumulation Factor: AUC (0–24 hr, day 15)/AUC (0–24 hr, day 1)	**Mean Peak Serum Concentration**	**Mean (SD) Post Steady-State Half-Life**
7-α-(thiomethyl) spirolactone (TMS)	1.25	391 ng/mL at 3.2 hr	13.8 hr (6.4) (terminal)
6-β-hydroxy-7-α-(thiomethyl) spirolactone (HTMS)	1.50	125 ng/mL at 5.1 hr	15.0 hr (4.0) (terminal)
Canrenone (C)	1.41	181 ng/mL at 4.3 hr	16.5 hr (6.3) (terminal)
Spironolactone	1.30	80 ng/mL at 2.6 hr	Approximately 1.4 hr (0.5) (β half-life)

The pharmacological activity of spironolactone metabolites in man is not known. However, in the adrenalectomized rat the antimineralocorticoid activities of the metabolites C, TMS, and HTMS, relative to spironolactone were 1.10, 1.28, and 0.32,

respectively. Relative to spironolactone, their binding affinities to the aldosterone receptors in rat kidney slices were 0.19, 0.86, and 0.06, respectively.
In humans, the potencies of TMS and 7-α-thiospirolactone in reversing the effects of the synthetic mineralocorticoid, fludrocortisone, on urinary electrolyte composition were 0.33 and 0.26, respectively, relative to spironolactone. However, since the serum concentrations of these steroids were not determined, their incomplete absorption and/or first-pass metabolism could not be ruled out as a reason for their reduced in vivo activities.
Spironolactone and its metabolites are more than 90% bound to plasma proteins. The metabolites are excreted primarily in the urine and secondarily in bile.
The effect of food on spironolactone absorption (two 100 mg spironolactone tablets) was assessed in a single-dose study of 9 healthy, drug-free volunteers. Food increased the bioavailability of un-metabolized spironolactone by almost 100%. The clinical importance of this finding is not known

INDICATIONS
AMIFRU-S is indicated in the treatment of oedematous states particularly in conditions where potassium ion conservation is important i.e.
• Congestive cardiac failure.
• Nephrotic syndrome.
• Ascites associated with liver cirrhosis.

AMIFRU-S is also indicated in the treatment of:
• Mild and moderate degrees of essential hypertension.
• In secondary hypertension AMIFRU-S is of value only as a symptomatic form of therapy and treatment should essentially be against the underlying cause.

CONTRAINDICATION
Furosemide
Furosemide is contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide.

Spironolactone
Spironolactone is contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, hyperkalemia, Addison's disease or other conditions associated with hyperkalemia, and with concomitant use of eplerenone.

WARNINGS AND PRECAUTIONS
Furosemide
WARNINGS
In patients with hepatic cirrhosis and ascites, furosemide therapy is best initiated in the hospital. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride

and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, furosemide should be discontinued.

Cases of tinnitus and reversible or irreversible hearing impairment and deafness have been reported. Reports usually indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, the use of higher than recommended doses, hypoproteinemia or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults, an infusion rate not exceeding 4 mg furosemide per minute has been used).

PRECAUTIONS

General

Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients.

As with any effective diuretic, electrolyte depletion may occur during furosemide therapy, especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop with furosemide, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids, ACTH, licorice in large amounts, or prolonged use of laxatives. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

All patients receiving furosemide therapy should be observed for these signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting. Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2-hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported.

In patients with severe symptoms of urinary retention (because of bladder emptying disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine. Thus, these patients require careful monitoring, especially during the initial stages of treatment.

In patients at high risk for radiocontrast nephropathy furosemide can lead to 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.

In patients with hypoproteinemia (e.g., associated with nephrotic syndrome) the effect of furosemide may be weakened and its ototoxicity potentiated.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated.

Patients allergic to sulfonamides may also be allergic to furosemide. The possibility exists of exacerbation or activation of systemic lupus erythematosus.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver or kidney damage, or other idiosyncratic reactions.

Laboratory Tests

Serum electrolytes (particularly potassium), CO_2, creatinine and BUN should be determined frequently during the first few months of furosemide therapy and periodically thereafter. Serum and urine electrolyte determinations are particularly important when the patient is vomiting profusely or receiving parenteral fluids. Abnormalities should be corrected or the drug temporarily withdrawn. Other medications may also influence serum electrolytes.
Reversible elevations of BUN may occur and are associated with dehydration, which should be avoided, particularly in patients with renal insufficiency.
Urine and blood glucose should be checked periodically in diabetics receiving furosemide, even in those suspected of latent diabetes.
Furosemide may lower serum levels of calcium (rarely cases of tetany have been reported) and magnesium. Accordingly, serum levels of these electrolytes should be determined periodically.
In premature infants furosemide may precipitate nephrocalcinosis/nephrolithiasis, therefore renal function must be monitored and renal ultrasonography performed.

Spironolactone
WARNINGS
Potassium supplementation
Potassium supplementation, either in the form of medication or as a diet rich in potassium, should not ordinarily be given in association with spironolactone therapy. Excessive potassium intake may cause hyperkalemia in patients receiving spironolactone.
Concomitant administration of spironolactone with the following drugs or potassium sources may lead to severe hyperkalemia:

- other potassium-sparing diuretics
- ACE inhibitors
- angiotensin II antagonists
- aldosterone blockers
- non-steroidal anti-inflammatory drugs (NSAIDs), e.g., indomethacin
- heparin and low molecular weight heparin
- other drugs known to cause hyperkalemia
- potassium supplements
- diet rich in potassium
- salt substitutes containing potassium

Spironolactone should not be administered concurrently with other potassium-sparing diuretics. Spironolactone, when used with ACE inhibitors or indomethacin, even in the presence of a diuretic, has been associated with severe hyperkalemia. Extreme caution should be exercised when spironolactone is given concomitantly with these drugs.
Hyperkalemia in patients with severe heart failure
Hyperkalemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving spironolactone. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium > 3.5 mEq/L. RALES excluded patients with a serum creatinine > 2.5 mg/dL or a recent increase in serum creatinine > 25%. The recommended monitoring for potassium and creatinine is one week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6

months. Discontinue or interrupt treatment for serum potassium > 5 mEq/L or for serum creatinine > 4 mg/dL.
Spironolactone should be used with caution in patients with impaired hepatic function because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Lithium generally should not be given with diuretics.

PRECAUTIONS

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance, e.g., hypomagnesemia, hyponatremia, hypochloremic alkalosis, and hyperkalemia.
Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities, which may be fatal. Consequently, no potassium supplement should ordinarily be given with spironolactone.
If hyperkalemia is suspected (warning signs include paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes.
If hyperkalemia is present, spironolactone should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These may include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.
Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.
Dilutional hyponatremia, manifested by dryness of the mouth, thirst, lethargy, and drowsiness, and confirmed by a low serum sodium level, may be caused or aggravated, especially when spironolactone is administered in combination with other diuretics, and dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of sodium, except in rare instances when the hyponatremia is life-threatening.
Spironolactone therapy may cause a transient elevation of BUN, especially in patients with pre-existing renal impairment. Spironolactone may cause mild acidosis.
Gynecomastia may develop in association with the use of spironolactone; physicians should be alert to its possible onset. The development of gynecomastia appears to be related to both dosage level and duration of therapy and is normally reversible when spironolactone is discontinued. In rare instances, some breast enlargement may persist when spironolactone is discontinued.

Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

Information for patients

Patients who receive spironolactone should be advised to avoid potassium supplements and foods containing high levels of potassium, including salt substitutes.

Laboratory tests

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals, particularly in the elderly and those with significant renal or hepatic impairments.

DRUG INTERACTION

Furosemide

Furosemide may increase the ototoxic potential of aminoglycoside antibiotics, especially in the presence of impaired renal function. Except in life-threatening situations, avoid this combination.

Furosemide should not be used concomitantly with ethacrynic acid because of the possibility of ototoxicity. Patients receiving high doses of salicylates concomitantly with furosemide, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, nephrotoxicity of nephrotoxic drugs such as cisplatin may be enhanced if furosemide is not given in lower doses and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Furosemide has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.

Lithium generally should not be given with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity.

Furosemide combined with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers may lead to severe hypotension and deterioration in renal function, including renal failure. An interruption or reduction in the dosage of furosemide, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers may be necessary.

Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Furosemide may decrease arterial responsiveness to norepinephrine. However, norepinephrine may still be used effectively.

Simultaneous administration of sucralfate and furosemide tablets may reduce the natriuretic and antihypertensive effects of furosemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved. The intake of furosemide and sucralfate should be separated by at least two hours.

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

Phenytoin interferes directly with renal action of furosemide. There is evidence that treatment with phenytoin leads to decrease intestinal absorption of furosemide, and consequently to lower peak serum furosemide concentrations.
Methotrexate and other drugs that, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of other drugs that undergo tubular secretion. High-dose treatment of both furosemide and these other drugs may result in elevated serum levels of these drugs and may potentiate their toxicity as well as the toxicity of furosemide.
Furosemide can increase the risk of cephalosporin-induced nephrotoxicity even in the setting of minor or transient renal impairment.
Concomitant use of cyclosporine and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperurecemia and cyclosporine impairment of renal urate excretion.
One study in six subjects demonstrated that the combination of furosemide and acetylsalicylic acid temporarily reduced creatinine clearance in patients with chronic renal insufficiency. There are case reports of patients who developed increased BUN, serum creatinine and serum potassium levels, and weight gain when furosemide was used in conjunction with NSAIDs.
Literature reports indicate that co-administration of indomethacin may reduce the natriuretic and antihypertensive effects of furosemide (furosemide) in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation. Patients receiving both indomethacin and furosemide should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved.

Spironolactone
ACE inhibitors
Concomitant administration of ACE inhibitors with potassium-sparing diuretics has been associated with severe hyperkalemia.
Angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin, and other drugs known to cause hyperkalemia
Concomitant administration may lead to severe hyperkalemia.
Alcohol, barbiturates, or narcotics
Potentiation of orthostatic hypotension may occur.
Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia, may occur.
Pressor amines (e.g., norepinephrine)
Spironolactone reduces the vascular responsiveness to norepinephrine. Therefore, caution should be exercised in the management of patients subjected to regional or general anesthesia while they are being treated with spironolactone.
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant may result.
Lithium
Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Nonsteroidal anti-inflammatory drugs (NSAIDs)

In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing, and thiazide diuretics. Combination of NSAIDs, e.g., indomethacin, with potassium-sparing diuretics has been associated with severe hyperkalemia. Therefore, when spironolactone and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Digoxin

Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. It may be necessary to reduce the maintenance and digitalization doses when spironolactone is administered, and the patient should be carefully monitored to avoid over- or under-digitalization.

Cholestyramine

Hyperkalemic metabolic acidosis has been reported in patients given spironolactone concurrently with cholestyramine.

Drug/Laboratory test interactions

Several reports of possible interference with digoxin radioimmunoassay by spironolactone, or its metabolites, have appeared in the literature. Neither the extent nor the potential clinical significance of its interference (which may be assay-specific) has been fully established

Carcinogenesis, Mutagenesis, Impairment of Fertility

Furosemide

Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. A small but significantly increased incidence of mammary gland carcinomas occurred in female mice at a dose 17.5 times the maximum human dose of 600 mg. There were marginal increases in uncommon tumors in male rats at a dose of 15 mg/kg (slightly greater than the maximum human dose) but not at 30 mg/kg.

Furosemide was devoid of mutagenic activity in various strains of Salmonella typhimurium when tested in the presence or absence of an in vitro metabolic activation system, and questionably positive for gene mutation in mouse lymphoma cells in the presence of rat liver S9 at the highest dose tested. Furosemide did not induce sister chromatid exchange in human cells in vitro, but other studies on chromosomal aberrations in human cells in vitro gave conflicting results. In Chinese hamster cells it induced chromosomal damage but was questionably positive for sister chromatid exchange. Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive. The urine of rats treated with this drug did not induce gene conversion in Saccharomyces cerevisiae.

Furosemide produced no impairment of fertility in male or female rats, at 100 mg/kg/day (the maximum effective diuretic dose in the rat and 8 times the maximal human dose of 600 mg/day).

Spironolactone

Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150, and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the

thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, 100, and 150 mg spironolactone /kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females.

A dose-related (above 20 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) for a period of one year. In two-year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular, and mammary tumors.

Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests in vitro. In the presence of metabolic activation, spironolactone has been reported to be negative in some mammalian mutagenicity tests in vitro and inconclusive (but slightly positive) for mutagenicity in other mammalian tests in vitro. In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests in vitro, inconclusive in others, and negative in still others.

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg spironolactone /kg/day, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, i.p.), spironolactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a two-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility, and fecundity. spironolactone (100 mg/kg/day), administered i.p. to female mice during a two-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, also increased the latency period to mating.

ADVERSE EFECTS

Furosemide

Adverse reactions are categorized below by organ system and listed by decreasing severity.

Gastrointestinal System Reactions

Hepatic encephalopathy in patients with hepatocellular insufficiency, pancreatitis, jaundice (intrahepatic cholestatic jaundice), increased liver enzymes, anorexia, oral and gastric irritation, cramping, diarrhea, constipation, nausea, vomiting.

Systemic Hypersensitivity Reactions
Severe anaphylactic or anaphylactoid reactions (e.g. with shock), systemic vasculitis, interstitial nephritis, and necrotizing angiitis.

Central Nervous System Reactions
Tinnitus and hearing loss, paresthesias, vertigo, dizziness, headache, blurred vision, xanthopsia.

Hematologic Reactions
Aplastic anemia, thrombocytopenia, agranulocytosis, hemolytic anemia, leukopenia, anemia, and eosinophilia.

Dermatologic-Hypersensitivity Reactions
Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, drug rash with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, exfoliative dermatitis, bullous pemphigoid, purpura, photosensitivity, rash, pruritis, urticaria.

Cardiovascular Reaction
Orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics, Increase in cholesterol and triglyceride serum levels.

Other Reactions
Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis, fever.

Whenever adverse reactions are moderate or severe, furosemide dosage should be reduced or therapy withdrawn.

Spironolactone
The following adverse reactions have been reported and, within each category (body system), are listed in order of decreasing severity.

Digestive: Gastric bleeding, ulceration, gastritis, diarrhea and cramping, nausea, vomiting.

Reproductive: Gynecomastia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, breast pain. Carcinoma of the breast has been reported in patients taking spironolactone but a cause and effect relationship has not been established.

Hematologic: Leukopenia (including agranulocytosis), thrombocytopenia.

Hypersensitivity: Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis.

Metabolism: Hyperkalemia, electrolyte disturbances.

Musculoskeletal: Leg cramps.

Nervous system /psychiatric: Lethargy, mental confusion, ataxia, dizziness, headache, drowsiness.

Liver / biliary: A very few cases of mixed cholestatic/hepatocellular toxicity, with one reported fatality, have been reported with spironolactone administration.

Renal: Renal dysfunction (including renal failure).

Skin: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, pruritis.

OVERDOSAGE

Furosemide

The principal signs and symptoms of overdose with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hypochloremic alkalosis, and are extensions of its diuretic action.

The acute toxicity of furosemide has been determined in mice, rats and dogs. In all three, the oral LD_{50} exceeded 1000 mg/kg body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats.

The concentration of furosemide in biological fluids associated with toxicity or death is not known.

Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy).

Hemodialysis does not accelerate furosemide elimination.

Spironolactone

The oral LD_{50} of spironolactone is greater than 1000 mg/kg in mice, rats, and rabbits.

Acute overdosage of spironolactone may be manifested by drowsiness, mental confusion, maculopapular or erythematous rash, nausea, vomiting, dizziness, or diarrhea. Rarely, instances of hyponatremia, hyperkalemia, or hepatic coma may occur in patients with severe liver disease, but these are unlikely due to acute overdosage. Hyperkalemia may occur, especially in patients with impaired renal function.

Induce vomiting or evacuate the stomach by lavage. There is no specific antidote. Treatment is supportive to maintain hydration, electrolyte balance, and vital functions.

Patients who have renal impairment may develop spironolactone-induced hyperkalemia. In such cases, spironolactone should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These may include the intravenous administration of calcium chloride solution, sodium bicarbonate

solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis

DOSAGES AND ADMINISTRATION

Depending on the condition, 1 to 8 tablets per day.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Furosemide

Pregnancy

PREGNANCY CATEGORY C - Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the maximal recommended human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Treatment during pregnancy requires monitoring of fetal growth because of the potential for higher birth weights.

The effects of furosemide on embryonic and fetal development and on pregnant dams were studied in mice, rats and rabbits.

Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (2 times the maximal recommended human dose of 600 mg/day). In another study, a dose of 50 mg/kg (4 times the maximal recommended human dose of 600 mg/day) also caused maternal deaths and abortions when administered to rabbits between Days 12 and 17 of gestation. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality that can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence and severity of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from the treated dams as compared with the incidence in fetuses from the control group.

Nursing Mothers

Because it appears in breast milk, caution should be exercised when furosemide is administered to a nursing mother.

Furosemide may inhibit lactation.

Pediatric Use

In premature infants furosemide may precipitate nephrocalcinosis/nephrolithiasis.

Nephrocalcinosis/nephrolithiasis has also been observed in children under 4 years of age with no history of prematurity who have been treated chronically with furosemide. Monitor renal function, and renal ultrasonography should be considered, in pediatric patients receiving furosemide.

If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Geriatric Use

Controlled clinical studies of furosemide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for the elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

Spironolactone
Pregnancy
Teratogenic effects
Pregnancy Category C
Teratology studies with spironolactone have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recommended human dose and, in the rabbit, approximates the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of resorption and a lower number of live fetuses in rabbits. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, spironolactone may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of male fetuses was observed. Offspring exposed during late pregnancy to 50 and 100 mg/kg/day doses of spironolactone exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, ovaries and uteri that were enlarged in females, and other indications of endocrine dysfunction, that spironolactone into adulthood. There are no adequate and well-controlled studies with spironolactone in pregnant women. Spironolactone has known endocrine effects in animals including progestational and antiandrogenic effects. The antiandrogenic effects can result in apparent estrogenic side effects in humans, such as gynecomastia. Therefore, the use of spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the fetus.
Nursing mothers
Canrenone, a major (and active) metabolite of spironolactone, appears in human breast milk. Because spironolactone has been found to be tumorigenic in rats, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. If use of the drug is deemed essential, an alternative method of infant feeding should be instituted.
Pediatric use
Safety and effectiveness in pediatric patients have not been established.

EXPIRY DATE

Should not be used later than expiry date.

STORAGE
Store in cool and dry place. Protect from light.

PRESENTATION
Available in a pack of as 5x3x10 Tablets.

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Windias health care (P) Ltd.
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