PRODUCT MONOGRAPH

[Pr] APO-FUROSEMIDE

Furosemide Tablets USP

20 mg, 40 mg and 80 mg

Diuretic

ATC Code: C03CA01

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Control No.: 172305

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Pr APO-FUROSEMIDE
(furosemide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 20 mg 40 mg 80 mg	**20 mg tablets:** colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. **40 mg and 80 mg tablets:** colloidal silicon dioxide, croscarmellose sodium, D & C Yellow # 10 Aluminum Lake 14-18% , lactose monohydrate, magnesium stearate, microcrystalline cellulose and Sunset Yellow Aluminum Lake 40% .

INDICATIONS AND CLINICAL USE

APO-FUROSEMIDE (furosemide) is indicated for:

- The treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease including, nephrotic syndrome, as well as other edematous states amenable to diuretic therapy.
- Can also be used alone in the control of mild to moderate hypertension, or in combination with other antihypertensive agents in more severe cases.

Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with furosemide alone.

Pediatrics

When administered to children, furosemide therapy should be instituted in the hospital, in carefully selected patients, under close observation with frequent monitoring of serum electrolytes (see DOSAGE AND ADMINISTRATION section).
The available pediatric data does not allow for a recommendation of a specific age range in this population.

Geriatrics (> 61 years of age)

Use in the geriatric population is associated with differences in safety (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

APO-FUROSEMIDE (furosemide) is contraindicated in:

- Patients who are hypersensitive to furosemide, sulfonamide-derived drugs or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.

- Patients with complete renal shutdown. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued.

- Patients with hepatic coma and precoma or in states of electrolyte depletion until the basic condition is improved or corrected. Therapy with APO-FUROSEMIDE should not be initiated in these patients (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic section).

- Severe hyponatremia, hypokalemia, hypovolemia, dehydration or hypotension must be regarded as contraindications until serum electrolytes and fluid balance and blood pressure have been restored to normal levels (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).

- As furosemide may be capable of displacing bilirubin from albumin at least "*in vitro*", it should not be administered to jaundiced newborn infants or to infants suffering from diseases (e.g., Rh incompatibility, familial non-hemolytic jaundice, etc.) with the potential of causing hyperbilirubinemia and possibly kernicterus.

- Women must not breast-feed if they are treated with furosemide (see WARNINGS AND PRECAUTIONS section).

WARNINGS AND PRECAUTIONS

General

APO-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 HAVE TO BE ADJUSTED TO THE INDIVIDUAL PATIENT'S NEEDS (SEE DOSAGE AND ADMINISTRATION).

All patients receiving APO-FUROSEMIDE therapy should be observed for signs and symptoms of fluid or electrolyte imbalance, hyponatremia, hypochloremic alkalosis, hypovolemia, hypomagnesemia, or hypocalcemia: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oligourea, tachycardia, arrhythmia, or gastro-intestinal disturbances such as nausea and vomiting, increases in blood glucose and alteration in glucose tolerance tests.

During long-term therapy a high-potassium diet is recommended. Potassium supplements may

be required especially when high doses are used for prolonged periods. Some electrolyte disturbances (e.g. hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome. Particular caution with potassium levels is necessary when the patient is on digitalis glycosides, potassium-depleting steroids, or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of furosemide therapy may be required.

Since rigid sodium restriction is conducive to both hyponatremia and hypokalemia, strict restriction in sodium intake is not advisable in patients receiving furosemide therapy. Urinary outflow must be secured. Patients with urinary outflow require careful monitoring-especially during the initial stages of treatment (see ADVERSE REACTIONS-Post-Market Adverse Drug Reactions-Renal and urinary disorders section).

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 (see CONTRAINDICATIONS section) and should therefore be avoided in elderly patients with dementia.

Carcinogenesis and Mutagenesis

Carcinogenicity: Furosemide in the approximate amount of 200 mg/kg body weight daily was administered to female mice and rats over a 2-year period with their diet. An increased incidence of mammary adenocarcinoma was noted in the mice, but not in the rats. These tumors occurred with a positive trend, and the incidence in the high dose group was increased compared to the control, in addition, the high-dose rate was about five fold over the historical rate. These tumors are considered to be associated with furosemide administration. This dose is considerably greater than the therapeutic dose administered in human patients.

In a carcinogenicity study, rats were administered furosemide in daily doses of 15 and 30 mg/kg body weight. Male rats in the 15 mg/kg-dose category, but not in the 30 mg/kg-dose category, showed a marginal increase in uncommon tumours.

Mutagenicity: In in-vitro tests on bacteria and mammalian cells, both positive and negative results have been obtained. Induction of gene and chromosome mutations, however, has been observed only where furosemide reached cytotoxic concentrations.

Ear/Nose/Throat

Cases of tinnitus and reversible deafness have been reported. There have also been some

reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness was usually insidious and gradually progressive up to 6 months after furosemide therapy. Hearing impairment is more likely to occur in patients with hypoproteinaemia or severely reduced renal function or in patients who are also receiving drugs known to be ototoxic. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons.

Endocrine and Metabolism

Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial blood sugar levels have been observed. Rare cases of precipitation of diabetes mellitus have been reported.

Asymptomatic hyperuricemia can occur and a gout attack may rarely be precipitated.

Hepatic/Biliary/Pancreatic

It may be advisable to hospitalize patients with hepatic cirrhosis and ascites prior to initiating therapy. 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 (see CONTRAINDICATIONS section).

Particularly careful monitoring is necessary in patients with hepatorenal syndrome.

Peri-Operative Considerations

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with APO-FUROSEMIDE and it is advisable to discontinue APO-FUROSEMIDE for 1 week prior to any elective surgery.

Special Populations

Pregnant Women

The teratogenic and embryotoxic potential of furosemide in humans is unknown. The drug should not be used in pregnant women or in women of childbearing potential unless in the opinion of the attending physician the benefits to the patient outweigh the possible risk to the fetus.

Reproductive and teratological studies have been performed in mice, rats, rabbits, cats, dogs and monkeys. With the exception of mice and rabbits, no abnormalities attributed to furosemide were detected. Furosemide caused unexplained maternal deaths and abortions in the rabbit at a daily dose of 50 mg/kg (approximately three times the maximum recommended human daily dose of 1000 mg orally) when administered between days 12 to 17 of gestation. In another study in rabbits, a dose of 25 mg/kg caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate foetal lethality which can precede maternal deaths.

The results of a mouse study and one of the three rabbit studies also showed an increased incidence of distention of the renal pelvis and, in some cases, of the ureters in foetuses derived from treated dams as compared to the incidence of foetuses from the control group.

Treatment during pregnancy requires monitoring of fetal growth.

Nursing Women

It should be noted that diuretics may partially inhibit lactation and that furosemide passes into the breast milk. Women must not breast-feed if they are treated with furosemide (see CONTRAINDICATIONS section).

Pediatrics

APO-FUROSEMIDE may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

In premature infants furosemide may precipitate nephrocalcinosis/nephrolithiasis. When administered to premature infants with respiratory distress syndrome in the first few weeks of life, diuretic treatment with furosemide may accentuate the risk of a patent ductus arteriosus (see WARNINGS AND PRECAUTIONS- Monitoring and Laboratory Tests section).

Caution is required in neonates because of prolonged half-life of furosemide.

Geriatrics (> 61 years of age)

Excessive diuresis induced by APO-FUROSEMIDE may result in dehydration and reduction of blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. APO-FUROSEMIDE may cause electrolyte depletion.

Furosemide binding to albumin may be reduced in elderly patients.

The drug is known to be substantially excreted unchanged 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 functions, care should be taken in dose selection and may be useful to monitor renal function.

In general dose selection for the elderly patients should be cautious, usually starting at the low end of dosage range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and the concomitant disease or other drug therapy.

Monitoring and Laboratory Tests

Frequent serum electrolyte, creatinine and CO2 content determinations should be performed during the first few months of therapy and periodically thereafter. It is essential to replace electrolyte losses and to maintain fluid balance so as to avoid any risk of electrolyte depletion (hyponatremia, hypochloremia, hypokalemia, hypomagnesemia or hypocalcemia), hypovolemia, or hypotension.

Checks on urine and blood glucose should be made at regular intervals especially in diabetics and in those suspected of latent diabetes when receiving furosemide. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial blood sugar levels have been observed.

Frequent BUN determinations during the first few months of therapy and periodically thereafter, as well as regular observations for possible occurence of blood dyscrasias, liver damage or

idiosyncratic reactions are advisable.

Particularly careful monitoring is necessary in:

- patients with hypoproteinaemia. Cautious dose titration is required.
- premature infants. Renal function must be monitored and renal ultrasonography performed.
- patients with hypotension
- patients who would be at particular risk from a pronounced fall in blood pressure (e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain).
- patients with hepatorenal syndrome.
- patients with latent and manifest diabetes mellitus
- patients with gout

Occupational Hazards

APO-FUROSEMIDE may lower the state of patient alertness and/or reactivity particularly at the start of treatment as a result of a reduction in blood pressure and of other adverse reactions (see ADVERSE REACTIONS section).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

No data available.

Post-Market Adverse Drug Reactions

Adverse reactions are categorized below by body system.

Blood and lymphatic system disorders

Anemia, eosinophilia, leukopenia and thrombocytopenia (with purpura) have occurred, as well as agranulocytosis, aplastic anemia and hemolytic anemia.

Ear and Labyrinth disorders

Cases of tinnitus and sometimes irreversible deafness have been reported. There have also been some reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness is usually insidious and gradually progressive up to 6 months after furosemide therapy. Hearing disorder is more likely to occur in patients with hypoproteinaemia or severely reduced renal function who are also receiving drugs known to be ototoxic.

Vertigo has been reported.

Eye disorders

Xanthopsia and blurred vision have been reported.

Gastrointestinal disorders

Acute pancreatitis, oral and gastric burning, diarrhea, nausea, vomiting and constipation have been reported. Rare occurrence of sweet taste has been reported.

Hepatobiliary disorders

Jaundice (intrahepatic cholestatic jaundice) and cholestasis have been reported.

Immune system disorders

Hypersensitivity reactions to furosemide also include photosensitivity, paresthesia and fever. Systemic hypersensitivity reactions include vasculitis and necrotizing angiitis.

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

Investigations

Increase in liver transaminases has been reported.

Transient elevations of BUN have been observed, especially in patients with renal insufficiency.

As with other diuretics, there may be an increase in serum creatinine, uric acid (this may lead to gout attack in predisposed patients), blood urea, cholesterol and triglyceride levels during furosemide treatment.

Metabolism and nutrition disorders

Electrolyte depletion has occurred during therapy with furosemide, especially in patients receiving higher doses with a restricted salt intake. Electrolyte depletion (hyponatremia, hypochloremia, hypokalaemia, hypocalcemia and hypomagnesemia) manifests itself by adverse reactions attributed to various body systems: weakness, dizziness, drowsiness, polyuria, polydipsia, orthostatic hypotension, lethargy, sweating, bladder spasms, anorexia, vomiting, mental confusion, meteorism, thirst, headache, muscle cramp, muscle weakness, tetany and disorder of cardiac rhythm (see WARNINGS AND PRECAUTIONS section).

The development of electrolyte disturbances (including symptomatic) is influenced by factors such as underlying diseases (e.g. liver cirrhosis, cardiac failure), concomitant medication and nutrition.

Cases of Pseudo-Bartter syndrome (hypochloremia, hypokalaemia, alkalosis, normal to low blood pressures, and elevated plasma renin and aldosterone) have been reported in the context of misuse and/or long-term use of furosemide.

Treatment with furosemide has occasionally caused some deterioration of metabolic control in cases of manifest diabetes, or has made latent diabetes manifest.

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.

Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated.

In extreme cases, hypovolemia may lead to dehydration, circulatory collapse, hemoconcentration and thrombophilia. Thrombophlebitis and emboli have been reported.

Nervous system disorders

At the commencement of treatment, excessive diuresis may give rise, especially in elderly patients, to a feeling of pressure in the head, dizziness.

Paresthesia has been reported.

Hepatic encephalopathy in patients with hepatocellular insufficiency has been reported.

Renal and urinary disorders

Symptoms of obstructed micturition (e.g. in hydronephrosis, prostatic hypertrophy, ureterostenosis) may become manifest or may be aggravated during medication with diuretics.

Interstitial nephritis has been reported.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur. Increases in urine sodium and chloride have also been reported.

There have been some reported cases of renal failure.

In premature infants furosemide may precipitate nephrocalcinosis/nephrolithiasis.

Skin and subcutaneous tissue disorders

Various forms of dermatitis (e.g. dermatitis bullous), including urticaria, erythema multiforme, pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pruritus, epidermolysis bullosa, AGEP (acute generalized exanthematous pustolosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have occurred.

Dermatologic reactions to furosemide also include purpura and rash.

Vascular disorders

Too vigorous diuresis may induce orthostatic hypotension or acute hypotensive episodes, which may cause signs and symptoms such as impairment of concentration and reactions, lightheadedness or orthostatic intolerance. There have been some reported cases of thrombosis.

When administered to premature infants with respiratory distress syndrome in the first few weeks of life, diuretic treatment with furosemide may accentuate the risk of a patent ductus arteriosus.

DRUG INTERACTIONS

Overview

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine or curare-type muscle relaxants (see WARNINGS AND PRECAUTIONS – Peri-Operative Considerations section).

In case of concomitant abuse of laxatives, the risk of an increased potassium loss should be considered.

Glucocorticoids, carbenoxolone and licorice may also increase potassium loss.

Administration of furosemide to diabetic patients may result in possible decrease of diabetic control. Dosage adjustments of the anti-diabetic agent may be needed.

Hearing impairment is more likely to occur in patients who are also receiving drugs known to be ototoxic (e.g. aminoglycosides antibiotics, ethacrynic acid and cisplatin) (see WARNINGS AND PRECAUTIONS section).

In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when APO-FUROSEMIDE is administered, since furosemide potentiates their hypotensive effect.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin, acetyl-salicylic acid) may attenuate the effect of APO-FUROSEMIDE and may cause renal failure in case of pre-existing hypovolemia.

Drug-Drug Interactions

The drug interactions discussed in this section are based on either drug interaction case reports, or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Established or Predicted Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	T	↓ furosemide diuretic effect	Anticonvulsant drugs (phenytoin, carbamazepine, phenobarbital), which, like furosemide, undergo significant renal tubular secretion, may also attenuate the effect of furosemide.
Antidiabetics			
Antidiabetics	T	↓ antidiabetic drug effect	The effects of antidiabetic drugs may be reduced.

Proper Name	Ref	Effect	Clinical Comments
Antihypertensive Agents			
ACE inhibitors	CT	↓ blood pressure and renal function	Especially in combination with ACE inhibitors, a marked hypotension may be seen sometimes progressing to shock. The concomitant administration of furosemide with ACE-inhibitors may lead to deterioration in renal function and, in isolated cases, to acute renal failure. Consideration must be given to interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor.
Angiotensin II receptor antagonists	CT	↓ blood pressure and renal function	Especially in combination with angiotensin II receptor antagonists, a marked hypotension may be seen sometimes progressing to shock. The concomitant administration of furosemide with angiotensin II receptor antagonists may lead to deterioration in renal function and, in isolated cases, to acute renal failure. Consideration must be given to interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an angiotensin II receptor antagonist.
Cephalosporins			
Cephalosporins	T	↓ renal function	Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.
Chloral Hydrate			
Chloral Hydrate	C	-	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.
Chlorothiazides			
Chlorothiazides	T	-	The concurrent use of furosemide with chlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.
Cisplatin			
Cisplatin	T	↑ nephrotoxicity ↑ ototoxicity	Nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment. There is also a risk of ototoxic effects if cisplatin and furosemide are given concomitantly.

Proper Name	Ref	Effect	Clinical Comments
Cyclosporine			
Cyclosporine	CT	-	Concomitant use of cyclosporine A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperurecemia and cyclosporine impairment of renal urate excretion.
Digitalis Glycosides			
Digitalis Glycosides	T	↓ potassium plasma concentration	Some electrolyte disturbances (e.g. hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome). Particular caution with potassium levels is necessary when the patient is on digitalis glycosides. Potassium supplementation, diminution in dose, or discontinuation of furosemide therapy may be required (see WARNINGS AND PRECAUTIONS).
Lithium			
Lithium	T	↑ lithium plasma concentration	Renal clearance of lithium is decreased in patients receiving furosemide, resulting in increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels be carefully monitored in patients receiving this combination.
Methotrexate			
Methotrexate	T	↓ furosemide diuretic effect	Methotrexate, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.
Nephrotoxic Drugs			
Nephrotoxic Drugs	T	↑ nephrotoxicity	The harmful effects of nephrotoxic drugs on the kidney may be increased.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)			
Indomethacin	CT	↓ furosemide diuretic effect	Clinical studies have shown that the administration of indomethacin can reduce the natriuretic and anti-hypertensive effect of furosemide in some patients. This response has been attributed to inhibition of prostaglandin synthesis by indomethacin. Therefore, when indomethacin is added to the treatment of a patient receiving furosemide, or furosemide is added to the treatment of a patient receiving indomethacin, the patient should be closely observed to determine if the desired effect of furosemide is obtained. Indomethacin blocks the furosemide-induced increase in plasma-renin activity. This fact should be kept in mind when evaluating plasma-renin activity in hypertensive patients.

Proper Name	Ref	Effect	Clinical Comments
Potassium-depleting Steroids			
Potassium-depleting Steroids	T	↓ potassium plasma concentration	Some electrolyte disturbances (e.g. hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome). Particular caution with potassium levels is necessary when the patient is on potassium-depleting steroids. Potassium supplementation, diminution in dose, or discontinuation of furosemide therapy may be required (see WARNINGS AND PRECAUTIONS).
Probenecid			
Probenecid	T	↓ furosemide diuretic effect	Probenecid, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.
Radiocontrast Agents			
Radiocontrast Agents	CT	↑ radiocontrast nephropathy	Patients who were at high risk for radiocontrast nephropathy treated with furosemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.
Risperidone			
Risperidone	CT	-	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. See PRECAUTIONS section, regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.
Salicylates			
Salicylates	T	↑ salicylate toxicity	Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competition for renal excretory sites.
Sucralfate			
Sucralfate	T	↓ furosemide absorption	Concurrent administration of furosemide and sucralfate should be avoided, as sucralfate reduces the absorption of furosemide from the intestine and hence weakens its effect.
Theophylline			
Theophylline	T	↑ theophylline effect	The effects of theophylline may be increased.

Legend: C= Case Study; CT= Clinical Trial; T= Theoretical

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal product have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Careful observations for changes in blood pressure must be made when APO-FUROSEMIDE is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50% as soon as APO-FUROSEMIDE is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of APO-FUROSEMIDE, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

Recommended Dose and Dosage Adjustment

Adults (oral)

Edema

The usual initial dose of APO-FUROSEMIDE is 40 to 80 mg. Ordinarily a prompt diuresis ensues and the starting dose can then be maintained or even reduced. If a satisfactory diuresis has not occurred within 6 hours, succeeding doses should be increased by increments of 20 to 40 mg, if necessary. Maximum daily dose: 200 mg. Once the effective single dose has been determined, it may be repeated 1 to 3 times a day.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which APO-FUROSEMIDE is given for 2 to 4 consecutive days each week. With doses exceeding 120 mg/day, careful clinical and laboratory observations are particularly advisable.

Hypertension

A dosage schedule of 20 to 40 mg twice daily is recommended. Individualized therapy is of great importance. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other antihypertensive agents, rather than to increase the dose of APO-FUROSEMIDE.

Pediatrics (oral)

APO-FUROSEMIDE therapy should be instituted in the hospital, in carefully selected patients, under close observation with frequent monitoring of serum electrolytes.

Orally, the initial dose should be in the range of 0.5 to 1.0 mg/kg body weight.

The total daily dose (given in divided doses of 6 to 12 hours apart) should not exceed 2 mg/kg orally. In the newborn and in pre mature babies, the daily dose should not exceed 1 mg/kg. An intermittent dosage schedule should be adopted as soon as possible using the minimum effective dose at the longest possible intervals. Particular caution with regard to potassium levels is always desirable when APO-FUROSEMIDE is used in infants and children.

OVERDOSAGE

Symptoms

Dehydration, electrolyte depletion and hypotension may be caused by overdosage or accidental ingestion. In cirrhotic patients, overdosage might precipitate hepatic coma.

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

Treatment

The drug should be discontinued and appropriate corrective treatment applied: 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).

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designed to reduce absorption (e.g. activated charcoal).

For management of a suspected drug overdose, contact your regional Poison Control Centre,

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Animal experiments using stop-flow and micropuncture techniques have demonstrated that furosemide inhibits sodium reabsorption in the ascending limb of Henle's loop as well as in both proximal and distal tubules. The action of furosemide on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone.

Furosemide may promote diuresis in cases which have previously proved resistant to other diuretics.

Pharmacodynamics

A continuous infusion of furosemide is more effective than repetitive bolus injections. Moreover, above a certain bolus dose of the drug there is no significant increase in effect.

The effect of furosemide is reduced if there is lowered tubular secretion or intra-tubular albumin binding of the drug.

Pharmacokinetics

Absorption

In man, furosemide is rapidly absorbed from the gastro-intestinal tract. The diuretic effect of furosemide is apparent within one hour following oral administration and the peak effect occurs in the first or second hour. The duration of action is 4-6 hours but may continue up to 8 hours. Following intravenous administration of the drug, the diuresis occurs within 30 minutes and the duration of action is about 2 hours.

Metabolism

A small fraction is metabolized by cleavage of the side chain.

Excretion

Urinary excretion is accomplished both by glomerular filtration and proximal tubular secretion, together this accounts for roughly only 2/3 of the ingested dose, the remainder being excreted in the feces.

The following table summarizes the elimination kinetics of furosemide.

Table 1 - Summary of furosemide's elimination kinetics.

Subjects	Route of Administration	Dose (mg)	Rate of Administration	Biliary Excretion	Max. Serum Concentration	$t_{½}$ (hr)
Normal	Oral	40	—	10-15%	< 1μg /mL	4.0
Normal	I.V.	40	Bolus	10-15%	2.5 μg/mL	4.5
Renal insufficiency	I.V.	1000	25 mg/min.	60%	53 μg /mL	13.5
Renal insufficiency	I.V.	1000	4 mg/min.	—	29 μg /mL	—

Special Populations and Conditions

Pediatrics: Depending on the maturity of the kidney, the elimination of furosemide may be slowed down. The metabolism of the drug is also reduced if the infant's glucuronisation capacity is impaired.

The terminal half-life is below 12 hours in infants with a post-conceptional age of more than 33 weeks.

In infants of 2 months and older, the terminal clearance is the same as in adults.

Geriatrics: The elimination of furosemide is slowed down due to reduced renal function in the elderly.

Gender: Data unavailable.

Race: Data unavailable.

Hepatic Insufficiency: In liver failure, the half-life of furosemide is increased by 30% to 90% mainly due to a larger volume of distribution. Additionally, in this patient group there is a wide variation in all pharmacokinetic parameters.

Renal Insufficiency: In renal failure, the elimination furosemide is slowed down and the half-life prolonged; the terminal half-life may be up to 24 hours in patients with severe renal failure.

In nephrotic syndrome the reduced plasma protein concentration leads to a higher concentration of unbound (free) furosemide. On the other hand, efficacy of furosemide is reduced in these patients due to binding to intratubular albumin and lowered tubular secretion.

Furosemide is poorly dialyzable in patients undergoing haemodialysis, peritoneal dialysis and CAPD.

Genetic Polymorphism: Data unavailable.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-FUROSEMIDE 20 mg: Each white, round, flat-faced tablet engraved 'APO' over '20' on one side contains furosemide 20 mg. Available in bottles of 100 and 1000. Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

APO-FUROSEMIDE 40 mg: Each yellow, round, flat-faced, scored tablet engraved 'APO' over '40' on one side contains furosemide 40 mg. Available in bottles of 100 and 1000. Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, D & C Yellow # 10 Aluminum Lake 14-18%, lactose monohydrate, magnesium stearate, microcrystalline cellulose and Sunset Yellow Aluminum Lake 40%.

APO-FUROSEMIDE 80 mg: Each yellow, capsule-shaped, flat-faced, partially scored tablet engraved 'APO 80' on one side contains furosemide 80 mg. Available in bottles of 100 and 500 tablets Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, D & C Yellow # 10 Aluminum Lake 14-18%, lactose monohydrate, magnesium stearate, microcrystalline cellulose and Sunset Yellow Aluminum Lake 40%.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

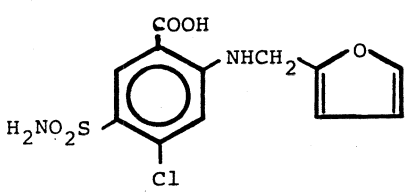
Drug Substance

Common name: Furosemide

Molecular Formula: $C_{12}H_{11}ClN_2O_5S$

Chemical Name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

Structural Formula:



Molecular Weight: 330.75 g/mol

Description: Furosemide is a white or almost white crystalline powder, which is odourless and almost tasteless. It is soluble in alcohol and ether and practically insoluble in water and chloroform.

CLINICAL TRIALS

No data available.

DETAILED PHARMACOLOGY

Furosemide has no significant pharmacological effects other than on the renal function.

Renal Pharmacology

In dogs, furosemide demonstrated diuretic properties. Diuresis and sodium excretion were induced by doses of 0.125 mg/kg administered intravenously or 0.5 mg administered orally.

Maximum water and sodium excretion is obtained by oral and intravenous doses of 12.5 and 25 mg/kg respectively. Increased potassium excretion can only be demonstrated with doses exceeding 1 mg/kg. The onset of action is rapid after intravenous and oral administration and the duration of activity is approximately 2 and 4 hours respectively.

Furosemide produces an immediate diuresis after intravenous administration and is effective unilaterally after injection into a renal artery. Its action, therefore, is directly on the kidney. The diuretic response is prompt and relatively brief. At the peak of diuretic response 30-40% of filtered sodium load may be excreted, along with some potassium and with chloride as the major anion. Furosemide augments the potassium output as a result of increased distal potassium secretion. Its diuretic action is independent of changes in acid-base balance. Under conditions of acidosis or alkalosis the diuretic produces chloruresis without augmentation of bicarbonate excretion. It does not inhibit carbonic anhydrase.

On the basis of changes in free-water production furosemide inhibits sodium reabsorption in the ascending limb of Helves loop. However, proximal sites of action are also involved, as determined by micropuncture. Partial distal inhibition of sodium reabsorption is also possible. It also decreases the urinary excretion of uric acid and prolonged administration may lead to hyperuricemia. Since urate is transported in the proximal tubule, the effect of the drug on uric acid excretion further suggests a proximal tubule site of action.

Administration of furosemide may induce extracellular metabolic alkalosis, primarily by virtue of the disproportionate loss of chloride, but also, in part, as a result of the variable depletion of potassium.

TOXICOLOGY

The acute toxicity of furosemide has been determined in four animal species:

Table 2 - **ACUTE TOXICITY (LD_{50}) OF FUROSEMIDE (Approximate doses in mg/kg)**

SPECIES	ORAL	INTRAVENOUS
Mice	1000	300
Adult Rats	4600	700
Newborn Rats	400	-
Rabbits	700	400
Dogs	2000	over 400

The acute toxicity was characterized by signs of vasomotor collapse, sometimes accompanied by slight convulsions. Surviving animals often became dehydrated and depleted of electrolytes. In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with furosemide were done in rats, dogs and monkeys.

1. **Rats:** A one-year study was performed on one hundred albino rats at dosages of 0, 50, 100, 200 and 400 mg/kg/day orally. Seventy-six rats survived for one year. Ten rats from the two highest dose groups died within the first 10 days of therapy. Histological examination of those animals dying early revealed striking basophilic degeneration of the myocardial fibers with infiltration and necrotic foci consistent with severe electrolyte imbalance.

   In the kidney, the most consistent pathological changes seen were degenerative changes in the tubular epithelium manifested by swollen cells with increased density of the cytoplasm. Occasionally, focal necrosis of the epithelium and decreased cell size were evident, plus accumulation of some calcified material. These changes were considered consistent with the nephropathy of potassium deficiency.

2. **Dogs:** In a six-month study, eighteen out of twenty beagle dogs survived oral daily doses of 0, 10, 30, 100 and 350 mg/kg. The most consistent pathological findings were renal lesions consisting of calcifications and scarring of the renal parenchyma at all doses above 10 mg/kg. The renal capsule above these lesions sometimes showed strikingly enlarged lymph vessels with thickened walls.

3. **Rhesus Monkeys:** In a 12-month study, daily oral doses of furosemide of 27 mg/kg and 60 mg/kg brought about pathological findings that consisted of dilated convoluted tubules with casts in 3 out of 20 animals given 27 mg/kg and in 6 out of 9 animals given 60 mg/kg. These lesions were considered drug related.

Reproductive and teratological studies

Reproductive and teratological studies have been performed in mice, rats, rabbits, cats, dogs and monkeys. With the exception of mice and rabbits, no abnormalities attributed to furosemide were detected. Furosemide caused unexplained maternal deaths and abortions in the rabbit at a daily dose of 50 mg/kg (approximately three times the maximum recommended human daily dose of 1000 mg orally) when administered between days 12 to 17 of gestation. In another study in rabbits, a dose of 25 mg/kg caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate foetal lethality which can precede maternal deaths.

The results of a mouse study and one of the three rabbit studies also showed an increased incidence of distention of the renal pelvis and, in some cases, of the ureters in foetuses derived from treated dams as compared to the incidence of foetuses from the control group.