PRODUCT MONOGRAPH

[Pr] FUROSEMIDE SPECIAL
Furosemide Injection USP

10 mg/mL

Diuretic

Sandoz Canada Inc.
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Boucherville, QC, Canada
J4B 7K8

Date of Revision: September 6, 2012

Control no. 153154

Furosemide Special
Furosemide Injection USP
250 mg/25 mL 10 mg/mL
Diuretic - Preservative Free

Diuretic restricted for patients with severely impaired renal function.
For IV infusion only.

CLINICAL PHARMACOLOGY

Furosemide is a potent, rapid-acting, nonthiazide, nonmercurial diuretic. Animal experiments utilizing micropuncture and stop flow techniques as well as various clearance studies in both humans and experimental animals have demonstrated that furosemide inhibits the reabsorption of electrolytes in the ascending limb of the loop of Henle. The drug also decreases reabsorption of sodium and chloride, and increases potassium excretion in the distal renal tubule and exerts a direct effect on electrolyte transport at the proximal tubule. Furosemide does not inhibit carbonic anhydrase and is not an aldosterone antagonist. Its diuretic action is independent of alterations in body acid-base balance.

After IV administration of furosemide, diuresis occurs within 5 minutes, reaches a maximum within 20–60 minutes and persists for approximately one to two hours; in patients with severely impaired renal function, the diuretic response may be prolonged by as much as eight hours. Patients exhibit large variability in diuretic response, with the half-lives ranging between 30-70 minutes (mean of 50 minutes).
Furosemide binds to plasma proteins. The elimination half-life is more prolonged in patients with advanced renal failure or concomitant liver disease; in the case of the former, the half-life was extended to 9.7 hours when 1 g of furosemide was administered IV.

Renal furosemide clearance averages 3.3 mL/minute in patients with advanced renal failure and is dependent upon the adequacy of renal function. Nonrenal furosemide clearance is increased to 35.7 mL/minute in the absence of liver disease but is reduced in patients with superimposed hepatic dysfunction.

INDICATIONS

Furosemide in high-dosage formulations (250 mg vials) is intended exclusively for patients with severely impaired renal function. For use under strict medical supervision only within a hospital setting (see DOSAGE AND ADMINISTRATION).

Furosemide Special (Furosemide Injection USP) is intended for use as an adjuvant in the treatment of oliguria and for the promotion of diuresis in the treatment of edema:

- in selected patients with acute renal failure, e.g. in the postoperative phase or in association with septic infections;

- in selected patients with chronic renal failure with fluid retention, both in the predialysis phase and when dialysis has become unavoidable, especially in the presence of acute pulmonary edema;
- in selected patients with nephrotic syndrome with severe impairment of renal function, e.g. in chronic glomerular nephritis, lupus erythematosus and Kimmelstiel-Wilson syndrome.

CONTRAINDICATIONS

Furosemide Special (Furosemide Injection USP) is contraindicated in patients with complete renal shutdown and a glomerular filtration rate below 5 mL/minute.
If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, discontinue furosemide. In hepatic coma, precoma or in states of electrolyte depletion, furosemide therapy should not be instituted until the underlying condition has been corrected or ameliorated.

Furosemide Special (Furosemide Injection USP) is contraindicated in patients with hepatic cirrhosis, renal failure due to poisoning with nephrotoxic or hepatotoxic substances, or with renal failure accompanied by hepatic coma.

Furosemide Special (Furosemide Injection USP) is contraindicated in patients with a known history of hypersensitivity to furosemide, sulfonamide-derived drugs or to any ingredient in the formulation or component of the container. For a complete listing, see Composition section of the product monograph. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.

Severe hypokalemia, hypovolemia or hypotension must be regarded as contraindications until serum potassium, fluid balance and blood pressure have been restored to normal levels.

Furosemide Special (Furosemide Injection USP) is contraindicated in patients whose glomerular filtration rate exceeds 20 mL/minute; in such cases, furosemide may cause extremely severe water and electrolyte loss.

WARNINGS

Furosemide Special (Furosemide Injection USP) is to be used under strict medical supervision and only within a hospital setting. 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; dose and dose schedule have to be adjusted to the individual patient's needs (see DOSAGE AND ADMINISTRATION).

During treatment with furosemide in high-dosage formulations (250 mg vials), extreme care must always be taken to adjust dosage to individual requirements. Rate of infusion must not exceed 4 mg/minute.

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 six months after furosemide therapy. Hearing impairment is more likely to occur in patients with hypoproteinemia or severely reduced renal function who are given large doses of furosemide parenterally, at a rate exceeding 4 mg/minute 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.

The teratogenic and embryotoxic potential of furosemide in humans is unknown. Because furosemide has been shown to produce fetal abnormalities in animal reproductive studies, it should not be used in pregnant women or in women of childbearing potential unless the benefits to the patient outweigh the possible risk to the fetus. Treatment during pregnancy requires monitoring of fetal growth.

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 furosemide therapy and it is advisable to discontinue furosemide for one week prior to any elective surgery.

Furosemide should be used with caution in patients with hepatic cirrhosis because rapid alterations in fluid and electrolyte balance and diuretic therapy may be related to the development of hepatorenal syndrome. 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.

Furosemide should not be administered to jaundiced newborn infants or to infants suffering from diseases which could potentially cause hyperbilirubinemia or kernicterus (e.g. Rh incompatability, familial nonhemolytic jaundice, etc.) because the drug may potentially displace bilirubin from albumin *in vitro*.

PRECAUTIONS

Excessive diuresis induced by 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.

Furosemide may cause electrolyte depletion. Patients should be observed for clinical signs of fluid or electrolyte disturbance. Frequent serum electrolyte and CO_2 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) and hypovolemia or hypotension. Serum glucose, uric acid, BUN and creatinine should be monitored occasionally.

During long-term therapy a high potassium diet is recommended. Potassium supplements may be required, especially with long-term administration of high doses. 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 concentrations is necessary when the patient is on digitalis glycosides, potassium depleting steroids, or in the case of infants and children. Potassium supplementation, a reduction in dose, or discontinuation of furosemide therapy may be necessary.

Since rigid sodium restriction is conducive to both hypokalemia and hyponatremia, strict restriction in sodium intake is not advisable in patients receiving furosemide.

In children, urge to defecate, complaints of abdominal pain and cramping have been reported after IV furosemide. An association of these symptoms with a low serum calcium and/or a low calcium:protein ratio is possible. Furosemide may lower serum calcium concentrations, and rare cases of tetany have been reported. Accordingly, periodic serum calcium concentrations should be obtained.

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some severely premature infants treated with IV furosemide for edema due to patent ductus arteriosus and hyaline membrane disease. The concurrent use of chlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.

Periodic checks on urine and blood glucose should be made in diabetics and even in those suspected of latent diabetes when receiving furosemide. Increases in blood glucose and alterations in glucose tolerance tests have been observed. Rare cases of precipitation of diabetes mellitus have been reported. Patients should be observed for possible decrease of diabetic control. If correction of the potassium deficit does not restore control, dosage adjustments of the antidiabetic agent may be needed.

Particularly careful monitoring is necessary in:

- patients with hypoproteinemia. Cautious dose titration is required.
- premature infants. Renal function must be monitored and renal ultrasonography must be performed
- patients who would be at a particular risk from a pronounced fall in blood pressure
- patients with hepatorenal syndrome

Frequent BUN and serum creatinine determinations as well as regular observations for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions are advisable.

Asymptomatic hyperuricemia can occur and, rarely, gout may be precipitated.

Since furosemide is a sulfonamide derivative, it should be used with caution in patients with known sulfonamide sensitivity.

It should be noted that diuretics may partially inhibit lactation and that furosemide passes into the breast milk.

DRUG INTERACTIONS

Drugs Affected by or Causing Potassium Depletion

Furosemide reportedly causes prolonged neuromuscular blockade in patients receiving nondepolarizing neuromuscular blocking agents (e.g. tubocurarine chloride, gallamine triethiodide), presumably because of potassium depletion or decreased urinary excretion of the muscle relaxant. Furosemide may also cause decreased arterial responsiveness to pressor amines (see WARNINGS).

Some drugs such as corticosteroids, corticotropin and amphotericin B also cause potassium loss, and severe potassium depletion may occur when one of these drugs is administered during furosemide therapy.

Warfarin: Sulfonamide diuretics may enhance the effect of warfarin.

Lithium: Diuretic therapy may increase lithium concentrations and enhance the cardiotoxic and neurotoxic (e.g. ataxia, confusion and mental disorientation) effects of lithium. If these drugs are administered concurrently, a dosage adjustment of lithium may be necessary and more frequent determinations of serum lithium concentrations are warranted to minimize potential toxicity, particularly when combined with sodium restriction.

Antidiabetic Agents: Administration of furosemide to diabetic patients may interfere with the hypoglycemic effect of insulin or oral antidiabetic agents (see PRECAUTIONS). Dosage adjustment of the anti-diabetic agent may be needed.

Antihypertensive Agents: The antihypertensive effect of these agents may be enhanced when given concomitantly with furosemide. 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.

Indomethacin: Clinical studies have shown that the administration of indomethacin can reduce the natriuretic and antihypertensive 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 regimen of a patient receiving furosemide or vice versa, 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 should be kept in mind when evaluating plasma-renin activity in hypertensive patients.

Other Drugs

Concomitant administration of furosemide and aminoglycoside antibiotics or other ototoxic drugs may result in increased incidence of ototoxicity. Concomitant use of these drugs should be avoided. In addition, the possibility that IV furosemide may increase aminoglycoside toxicity by altering serum and tissue concentrations of the antibiotic should be considered. It has been proposed, but not proven, that furosemide may enhance the nephrotoxicity of neomycin and cephaloridine; concurrent administration of these drugs is therefore not advisable.

It has been reported in the literature that diuretics such as furosemide may enhance the nephrotoxicity of cephalosporins. Therefore the simultaneous administrations of these drugs with furosemide is not advisable.

Furosemide and salicylates reportedly have competitive renal excretory sites and, therefore, patients receiving high doses of salicylates with furosemide may experience salicylate toxicity at lower dosage than usual.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin, acetyl-salicylic acid) may attenuate the effect of furosemide and may cause renal failure in case of pre-existing hypovolemia. Probenecid and anticonvulsant drugs (phenytoin, carbamazepine, phenobarbitone) may also attenuate the effect of furosemide.

Epileptic patients receiving chronic anticonvulsant therapy (e.g. phenobarbital, phenytoin) may have a reduced diuretic response to furosemide as compared to controls. It has been postulated that renal sensitivity to furosemide is diminished by antiepileptic drugs.

ADVERSE REACTIONS

Fluid, Electrolyte, Cardiovascular and Renal Effects

Electrolyte depletion has occurred during therapy with furosemide, especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion 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 cardiac rhythm disorders. (See PRECAUTIONS).

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.

Excessive diuresis induced by Furosemide Special 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.

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

Furosemide increases calcium excretion; rarely, tetany has been reported.

Transient elevations of BUN have been observed, especially in patients with renal insufficiency. Large IV doses of furosemide may cause temporary uricosuria. Blood ammonia concentrations may be increased, especially in patients with preexisting elevations of blood ammonia.

Otic Effects
Tinnitus or reversible deafness have been reported. Permanent deafness has occurred, mainly in children undergoing renal transplantation. The onset of deafness in these cases was usually insidious and gradually progressive up to 6 months after furosemide therapy. Patients with severely reduced renal function who are given large parenteral doses of furosemide at rates exceeding 4 mg/min., or patients also receiving drugs known to be ototoxic, are more likely to sustain hearing impairment.

GI Effects
Adverse GI effects of furosemide include nausea, anorexia, oral and gastric irritation, vomiting, cramping, diarrhea and constipation. In children, urge to defecate and complaints of mild to moderate abdominal pain have been reported after furosemide was administered IV (see PRECAUTIONS).
In addition, rare occurrences of sweet taste have been reported, but a causal relationship to the drug has not been established.

Metabolic Effects
Furosemide may produce hyperglycemia and glycosuria, possibly as a result of hypokalemia, in patients with predisposition to diabetes. Treatment with furosemide has occasionally caused a deterioration in cases of manifest diabetes or made latent diabetes mellitus manifest.

Nervous System Effects
Adverse nervous system effects of furosemide include dizziness, lightheadedness, vertigo, headache, xanthopsia, blurred vision and paresthesias.

Hematologic Effects
Anemia, eosinophilia, leukopenia, neutropenia and thrombocytopenia (with purpura) have occurred in patients receiving furosemide. In addition, rare cases of agranulocytosis and aplastic anemia have been reported which responded to treatment.

Dermatologic and Hypersensitivity Reactions
Adverse dermatologic and/or hypersensitivity reactions to furosemide include purpura, photosensitivity, rash, urticaria, pruritus, exfoliative dermatitis, erythema multiforme, epidermolysis bullosa and necrotizing angiitis (vasculitis, cutaneous vasculitis). Patients with known sulfonamide sensitivity may show allergic reactions to furosemide.
Severe anaphylactic and anaphylactoid reactions (e.g. with shock) occur rarely.

Local Effects
Thrombophlebitis and emboli have occurred with IV administration.

Endocrine Effects
It has been demonstrated that furosemide in high concentrations can inhibit T4 binding in plasma. Although the clinical significance of these findings remain to be established, such an effect may be a factor in contributing to the development of low T4 state in critical illness.

Other
Adverse effects of furosemide include increased perspiration, weakness, restlessness, muscle spasm, urinary bladder spasm and urinary frequency. Bladder spasms may be caused by formation of calcium-containing crystals in the urine.

Intrahepatic cholestatic jaundice and pancreatitis have also occurred in patients receiving furosemide. Furosemide may possibly exacerbate or activate systemic lupus erythematosus.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms
Dehydration, electrolyte depletion and hypotension may be caused by overdosage. In cirrhotic patients, overdosage may precipitate hepatic coma.

Treatment
Discontinue the drug. Replace 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).. Furosemide is not removed by hemodialysis.

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

DOSAGE AND ADMINISTRATION

Furosemide Special (Furosemide Injection USP) should not be added into the tubing of a running infusion solution. It should also not be mixed with any other drugs in the infusion container.
Do not use injection if solution is yellow.

For IV infusion, furosemide should be diluted with an infusion solution of sodium chloride 0.9%, lactated Ringer's or dextrose 5% injection. Furosemide may precipitate in and therefore is incompatible with solutions in which the resulting pH is less than 5.5. IV admixtures of Furosemide Special (Furosemide Injection USP) should be used within 24 hours after preparation.

Furosemide Special (Furosemide Injection USP) should be administered as a controlled infusion at a rate not exceeding 4 mg/minute in adults.

Changes in blood pressure should be carefully monitored when 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 furosemide is added to the regimen to prevent an excessive drop in blood pressure. As blood pressure falls under the potentiating effects of furosemide, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

Parenteral administration of furosemide should be replaced by oral therapy as soon as possible.

When furosemide is used in high doses, careful attention must be paid to the following points:

- if the patient is in shock, hypovolemia and hypotension must be corrected by appropriate measures before starting therapy;
- any serious abnormalities of serum electrolytes or acid-base balance must be corrected beforehand;
- when treating patients with conditions likely to interfere with micturition, such as prostatic hypertrophy or disturbed consciousness, it is absolutely essential to ensure free urinary drainage;
- because of the wide and unpredictable individual variations in responsiveness, it is important to adjust dosage to individual needs;
- once the desired rise in urinary output has begun, exact balance of water intake and water output must be maintained throughout the course of treatment so as to avoid hypovolemia or hypotension. Careful electrolyte replacement is also necessary.

Dosage

Furosemide Special (Furosemide Injection USP) is intended exclusively for selected patients with severely impaired glomerular filtration (GFR of less than 20 mL/minute but greater than 5 mL/minute) who have not responded to conventional doses of furosemide.

When high-dose furosemide infusions are used, dosage should be individualized according to patient response, titrating the dosage to gain maximum therapeutic effect while using the lowest possible effective dosage; the patient should be closely observed during therapy.

The dosage of Furosemide Special (Furosemide Injection USP) given below is for adults only. The dosage regimen for children has not yet been determined. The administration of large doses of furosemide in children has been associated with permanent deafness (see WARNINGS).

If a conventional single dose of 40–80 mg intravenously fails to produce an adequate diuresis within 30 minutes, infusion treatment with Furosemide Special (Furosemide Injection USP) 250 mg may be started.

Initial Dose
250 mg (25 mL vial) mixed with 250 mL of a suitable solution (see above) is given by intravenous infusion **at a rate not exceeding 4 mg/minute. (Infusion time for 275 mL is approximately one hour.)**

Additional Dose
Should the initial dose fail to produce an adequate increase (at least 40–50 mL per hour) in urinary output, a second infusion of 500 mg (appropriately diluted) should be started one hour after the conclusion of the first. The duration of this infusion is determined by the maximum rate of 4 mg furosemide per minute.

For hypervolemic patients, it is advisable to give Furosemide Special (Furosemide Injection USP) undiluted, or in suitable volume (e.g. 250 mg in 50 mL of infusion fluid) so as to avoid the risk of overhydration. **Intravenous infusions of the undiluted solution must be given with the aid of an electronic precision administration device so as to make sure that the upper limit of 4 mg furosemide (0.4 mL) per minute is not exceeded.**

If the satisfactory diuretic response is achieved (40–50 mL/hour), the effective dose can be repeated every 24 hours. However, a maximum daily dose of 1000 mg Furosemide Special (Furosemide Injection USP) should not be exceeded.

The criterion of optimal dosage is a urinary output of at least 2.5 litres per day.

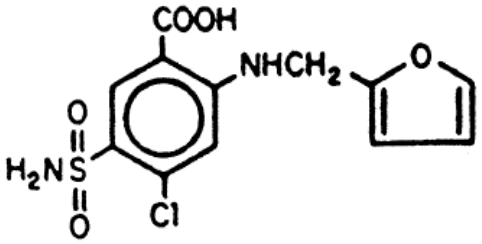
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Furosemide

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

Structural Formula:



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

Molecular Weight: 330.8

Description: White to yellowish white crystalline powder soluble in acetone, dimethylformamide, dilute alkalis, and ethanol, slightly soluble in water, with a melting range of 202 to 205°C (with decomposition).

COMPOSITION

Each mL of Furosemide Special (Furosemide Injection USP) contains 10 mg furosemide, sodium hydroxide for pH adjustment and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 and 30°C. Discard unused portion.
Preservative Free.

AVAILABILITY

Furosemide Special (Furosemide Injection USP) is available in 25 mL amber glass vials, boxes of 10.

PHARMACOLOGY

Renal Pharmacology: In dogs, diuresis and sodium excretion were induced by furosemide at doses of 0.125 mg/kg IV or 0.5 mg/kg PO; maximum effects were obtained at doses of 12.5 and 25 mg/kg respectively. Increased potassium excretion was only observed at doses exceeding 1 mg/kg. The onset of action was rapid after both routes of administration. The duration of activity is approximately two hours after intravenous administration and four hours after oral administration respectively.

Furosemide is effective after injection into the renal artery, indicating that it acts directly on the kidney. In humans, furosemide diuresis results in enhanced excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium, ammonium, bicarbonate and possibly phosphate; urinary total catecholamine excretion is also increased. In patients with normal renal function, the diuretic response is similar following oral or IV administration of equal doses of furosemide. In one study in uremic patients, however, diuresis and urinary excretion of sodium and potassium were greater after IV administration of furosemide than after equal oral doses.

TOXICOLOGY

(See existing Product Monograph for low dose furosemide).

Acute Toxicity

Species	**Intravenous LD_{50}**
Mice	300 mg/kg
Adult Rats	700 mg/kg

Signs of toxicity included vasomotor collapse, sometimes accompanied by slight convulsions. Surviving animals often became dehydrated and depleted of electrolytes. Most animals exhibited reduced motor activity, muscular weakness, ataxia and bradypnea.

Furosemide has been reported to be more toxic in newborn than adult rats.

Chronic Toxicity

Rats

A one-year study was performed on 100 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 ten days of therapy. Discharge from the eye, lethargy, anorexia, dyspnea and weight loss have been observed in animals receiving 200 mg/kg and 400 mg/kg doses. One death in the 100 mg/kg, two in the 200 mg/kg and ten in the 400 mg/kg groups occurred. Histological examination of those animals dying early revealed striking basophilic degeneration of the myocardial fibres with infiltration and necrotic foci consistent with severe electrolyte imbalance.

There was a significant, dose-related increase in the relative weight of the kidneys. The most consistent pathological changes seen in the kidney were degenerative changes in the tubular epithelium manifested by swollen cells with increased density of the cytoplasm. This lesion was

seen most often in the two highest dose groups but only rarely in the other groups. 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.

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. Levels of blood sugar and urea nitrogen were elevated in the animals treated with the highest doses; two of the four dogs in that group died. The highest dose was subsequently reduced to 250 mg/kg Urinalysis remained normal throughout the investigation except for urinary volume, creatinine and electrolyte levels. These changes are in keeping with the action of a diuretic drug.

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. There was no significant or consistent effect on organ weight.

Monkeys
In a 12-month study in Rhesus monkeys, 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.

Furosemide exhibited no teratogenic effect on dogs or rats.

Irritation Studies: Intravenous and intramuscular injections of 0.1 mL of furosemide injection were given twice daily to rabbits weighing between 1500 and 3000 g for five consecutive days.

In the animals injected intravenously, a slight increase in size and redness in the injected vein was noted as well as a slight edema in the ear.

Redness at the site of injection was observed in the animals injected intramuscularly.

REFERENCES

1. American Hospital Formulary Service, Drug Information, 1988: Furosemide Monograph, pp. 1456-1460.

2. Birtch AG, Zakheim RM, Jones LG, Barger AC. Redistribution of renal blood flow produced by furosemide and ethacrynic acid. Circulation Research, 1967; XXI: 869-878.

3. Brenner BM, Keimowitz RI, Wright FS, Berliner RW. An inhibitory effect of furosemide on sodium reabsorption by the proximal tubule of the rat nephron. J Clin Investigation, 1969; 48: 290-300.

4. Brown CB, Ogg CS, Cameron JS. High dose furosemide in acute renal failure: a controlled trial. Clin Nephrol, 1981; 15: 90-96.

5. Compendium of Pharmaceuticals and Specialties, 1989. Furosemide Monograph, pp. 414-415.

6. Hook JB, Blatt AH, Brody MJ, Williamson HE. Effects of several saluretic-diuretic agents on renal hemodynamics. J Pharmacol Experimental Therapeutics, 1966; 154(3): 667-673.

7. Knoben JE, Anderson PO. Handbook of clinical drug data. Fifth edition, 1983: 518-520.

8. Kuhnel HJ, Gunther K, Stein G, Hoffmann-Traeger A. Pharmacokinetics and pharmacodynamics of high-dose furosemide in patients with chronic renal failure or nephrotic syndrome. Int J Clin Pharm Tox, 1987; 25: 616-621.

9. Morelli OH, Moledo LI, Alanis E, Gaston OL, Terzaghi O. Acute effects of high dose furosemide in patients with chronic renal failure. Postgrad Med J, 1971; April Suppl: 29-35.

10. Morrin PAF. The effect of furosemide, a new diuretic agent, on renal concentrating and diluting mechanisms. Can J Physiology & Pharmacology, 1966; 44: 129-137.

11. Ogiso T, Iwaki M, Konishi Y. Effect of furosemide on plasma clearance, anticoagulant effect and protein binding of warfarin in rats. J Pharm Dyn, 1982; 5: 829-840.

12. Quick CA, Hoppe W. Permanent deafness associated with furosemide administration. Ann Otol, 1975; 84: 94-101.

13. Stein JH, Wilson CB, Kirkendall WM. Differences in the acute effects of furosemide and ethacrynic acid in man. J Lab & Clin Med, 1968; 7(4): 654-665.

14. Stockgit JR, Lim CF, Barlow JW, Stevens V, Topliss DJ, Wynne KN. High concentrations of furosemide inhibit serum binding and thyroxine. J Clin Endocrinol Metab, 1984; 59: 62-66.

15. Sanofi-aventis Canada Inc., Product Monograph, LASIX (furosemide tablets USP) Tablets 20 mg, 40 mg, Control #151334, Date of Revision: February 14, 2012.

16. Sandoz Canada Inc. Product Monograph, Furosemide Special SDZ, Control #154358, Date of Revision: June 1, 2012.