

**Composition****Urix Tablet**

Each tablet contains Furosemide 40 mg.

**Urix Injection**

Each ampoule contains Furosemide 20 mg

**Action**

Furosemide, an anthranilic acid derivative, is a loop diuretic having a rapid effect. Investigations into its mode of action have utilized micropuncture studies in both human and experimental animals and stop flow experiments in dogs. It is reported to exert inhibiting effects on electrolyte reabsorption in the proximal and distal renal tubules and especially in the ascending loop of Henle. The net effect is to enhance excretion of sodium, potassium and chloride ions, and water. Furosemide has no effect on carbonic anhydrase. Furosemide has a steep dose-response curve and wide therapeutic range.

In addition to its diuretic actions, furosemide has been shown to increase peripheral venous capacitance and reduce forearm blood flow. It also reduces renal vascular resistance with a resultant increase in renal blood flow the degree of which is proportional to the initial resistance. Furosemide may be effective in patients with moderate renal insufficiency.

Onset of diuresis following oral administration is within one hour, with peak effect occurring between 1-2 hours. Duration of effect is 6-8 hours. After intravenous administration, the onset of diuresis is within 5 minutes and somewhat later after intramuscular injection. Duration of effect is approximately 2 hours.

**Pharmacokinetics**

Approximately 60 to 70% of an oral dose of furosemide is absorbed. Peak plasma concentrations occur 60 minutes after oral administration and 30 minutes after intramuscular injection. They increase with increasing dose. Administration after food apparently delays absorption producing lower but more persistent blood concentrations. Plasma protein binding of furosemide to albumin is between 95-99%, however, the response to furosemide is determined more by the medicine concentration in the tissue compartment than that in the plasma.

Furosemide is excreted in the urine mainly as unchanged furosemide but glucuronide and free amine metabolites appear. The site of metabolism of the glucuronide metabolite is unknown. Approximately 80% of a dose appears in the urine within 24 hours. The terminal half-life is approximately 2 hours. Non-renal elimination also occurs especially in renal failure. Furosemide crosses the placental barrier and is excreted in milk. Absorption is reduced to 43 - 46% in patients with end-stage renal disease, and is probably reduced in patients with edematous bowel caused by congestive heart failure or nephrotic syndrome; parenteral administration may be preferable in these patients.

**Indications**

- Treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease, including the nephrotic syndrome.
- Adjunctive therapy in acute pulmonary edema.
- Treatment of hypertension.

**Contraindications**

- Known hypersensitivity to furosemide or sulphonamides.
- Renal failure due to nephrotoxic or hepatotoxic agents.
- Renal failure associated with hepatic coma.
- Anuria.

## Warnings

In patients with hepatic cirrhosis and ascites, initiation of therapy with furosemide is best carried out in hospital. In hepatic coma and 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, the drug should be discontinued.

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

## Pregnancy

### *Category C*

Safety of use in pregnancy has not been established. Furosemide should be used during pregnancy only if the potential benefits to the mother outweigh the potential risk to the fetus.

## Nursing Mothers

Furosemide appears in breast milk. Therefore, having taken into account the importance of the drug to the mother, either discontinue nursing or discontinue the drug.

## Adverse Reactions

### Gastro-intestinal

Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, intra-hepatic cholestatic jaundice and pancreatitis.

### Central Nervous System

Dizziness, vertigo, paraesthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss.

### Hematological

Anemia, leukopenia, thrombocytopenia, agranulocytosis (rare) and aplastic anemia (rare).

### Dermatological

Purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme and pruritus.

### Cardiovascular

Thrombophlebitis, orthostatic hypotension.

### Miscellaneous

Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness and urinary bladder spasm. Blood urea nitrogen (BUN) levels may be increased. Serum calcium, magnesium, potassium and sodium levels may be decreased.

## Precautions

Excessive diuresis may result in dehydration and reduction in blood volume with circulatory collapse, together with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Electrolyte depletion may occur during therapy, especially in patients receiving higher doses and a restricted salt intake. Frequent serum electrolyte, CO<sub>2</sub> and BUN determinations should be performed during the first few months of therapy and periodically thereafter, in order to correct abnormalities or if necessary, withdraw the drug temporarily.

Furosemide may lower serum calcium levels, and rare cases of tetany have been reported.

Accordingly, periodic serum calcium levels should be obtained.

All patients receiving furosemide therapy should be observed for the following signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis or hypokalemia): 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.

Asymptomatic hyperuricemia can occur, and gout may rarely be precipitated. Patients allergic to sulphonamides may also be allergic to furosemide. The possibility exists of exacerbation or activation of systemic lupus erythematosus.

## **Drug Interactions**

### *Furosemide/ Other Antihypertensive Drugs*

Furosemide may intensify the therapeutic effect of other antihypertensive drugs.

### *Furosemide/ Aminoglycoside Antibiotics*

Furosemide may increase the ototoxic and nephrotoxic potential of aminoglycoside antibiotics.

### *Furosemide/ Cardiac Glycosides*

Concurrent use may increase the possibility of digitalis toxicity associated with hypokalemia.

### *Furosemide/ Cephaloridine or Cephalothin*

Concurrent use may increase the potential for nephrotoxicity.

### *Furosemide/ Hypoglycemics*

Furosemide may raise blood glucose levels or interfere with the hypoglycemic effects of these agents. For adult-onset diabetics, dosage adjustment of hypoglycemic medications may be necessary during and after therapy.

### *Furosemide/ Antigout Medications*

Furosemide may raise the level of blood uric acid. Dosage adjustment of antigout medications may be necessary to control hyperuricemia and gout.

### *Furosemide/ Corticosteroids or Corticotropin (ACTH)*

Concurrent use may intensify electrolyte imbalance, particularly hypokalemia.

### *Furosemide/ Lithium Salts*

Concurrent use may provoke lithium toxicity because of reduced renal clearance. It is not recommended unless the patient can be closely monitored.

### *Furosemide/ Salicylates*

Concurrent use of high doses of salicylates with furosemide may lead to salicylate toxicity, because of competition at renal excretory sites.

### *Furosemide/ Alcohol/ Barbiturates/ Narcotics*

Alcohol, barbiturates or narcotics may aggravate orthostatic hypotension due to furosemide.

### *Furosemide/ Indomethacin*

Literature reports indicate that co administration of indomethacin may reduce the natriuretic and antihypertensive effects of 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.

## **Dosage and Administration**

Since furosemide is a potent diuretic that, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion, careful medical supervision is required. Dosage should be adjusted to the individual needs of each patient.

### **Edema**

The usual initial dosage of furosemide is 20-80 mg/day, administered as a single dose. Usually, prompt diuresis ensues. Depending on the response, a second dose should be administered 6-8 hours later. If the diuretic response is unsatisfactory, the dose should be increased by increments of 20 or 40 mg, no sooner than 6-8 hours after the previous dose, until the desired diuretic effect has been obtained. This individually determined dose should then be administered 1-2 times a day. In patients with severe edema, dosage may be titrated up to 600 mg/day. Mobilization of edema may be most efficiently and safely accomplished with an intermittent dosage schedule. Furosemide should be administered on 2-4 consecutive days, each week. With doses exceeding 80 mg/day, clinical and laboratory observations are recommended.

### **Hypertension**

The usual initial dosage is 40 mg, twice a day. Dosage should be adjusted according to response. If a patient does not respond, other antihypertensive agents should be added. Blood pressure changes should be observed when used with other antihypertensive, especially during initial therapy. The dosage of other agents should be reduced by at least 50% as soon as furosemide is added, to prevent excessive drop in blood pressure. As blood pressure falls, either the dose should be reduced or the other antihypertensives discontinued.

### **Infants and Children**

The usual initial dose of furosemide in infants and children is 2 mg/kg body weight. If the diuretic response after the initial dose is unsatisfactory, dosage may be increased by 1-2 mg/kg body weight, but no sooner than 6-8 hours after the first dose. Doses greater than 6 mg/kg body weight are not recommended. For maintenance therapy, the dose should be adjusted to the minimum effective level.

### **Over Dosage**

#### **Manifestations**

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

#### **Treatment**

Treatment of over dosage 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.

### **Presentation**

#### **Urix Tablet**

Box of 20 tablets

#### **Urix Injection**

Box of 5 ampoules