Furosemide Tablets, USP
20, 40, and 80 mg
Rx only

WARNING
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 (see DOSAGE AND ADMINISTRATION).

DESCRIPTION
Furosemide is a diurhetic which is an uricosuric and diuretic agent. Furosemide Tablets for oral administration contain furosemide as the active ingredient and the following inactive ingredients: corn starch, NF; lactose monohydrate, NF; pregelatinized corn starch, NF; talc, USP; and vitamin A palmitate. The structural formula is as follows:

\[
\text{Cl}_{2} \text{H}_{17}\text{NNO}_{2}\text{S}
\]

M.W. \(= 390.75\)

Tested by USP Dissolution Test 1.

CLINICAL PHARMACOLOGY
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 human 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 dietary NaCl intake, aldosterone and arildosterone.

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 range from 1 to 400 ng/mL in 95% to 98% bound in healthy individuals. The extent of binding may vary with coadministered therapeutic agents. The onset of diuresis following oral administration is within 1 to 2 hours. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

In furosemide, the unbound fraction is 8.7% at therapeutic concentrations in plasma. Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations range from 1 to 400 ng/mL in 95% to 98% bound in healthy individuals. The extent of binding may vary with coadministered therapeutic agents. The onset of diuresis following oral administration is within 1 to 2 hours. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

For patients with hepatic cirrhosis and ascites, the use of higher than recommended doses, hypoproteinemia or concomitant therapy with diuretics and/or potassium-losing agents may be necessary to achieve adequate利尿. Potassium supplements or diet may be needed to maintain serum potassium levels. Potassium supplements should be administered cautiously in patients with diabetes mellitus or those receiving potassium-sparing agents. The use of furosemide in patients receiving potassium-sparing agents may cause hyperkalemia. The use of furosemide in patients receiving beta blockers may result in some degree of hypokalemia, and the use of furosemide with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers may be associated with a higher incidence of hyperkalemia. The use of furosemide with beta blockers may result in some degree of hypokalemia, and the use of furosemide with angiotensin II receptor blockers may be associated with a higher incidence of hyperkalemia.

No international validation of furosemide from furosemide tablets and furosemide oral solution is 64% and 60%, respectively, of that of an intravenous injection of the drug. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (97 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but time-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 N 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.

Geriatric Population
Furosemide binding to albumin may be reduced in elderly patients. Furosemide is predominantly excreted unchanged in the urine. The renal clearance of furosemide after oral administration in healthy elderly male subjects (60 to 70 years of age) is statistically significantly lower than in younger healthy male subjects (20 to 35 years of age). The initial diuretic effect of furosemide in older subjects is decreased relative to younger patients (see PRECAUTIONS: Geriatric Use).

INDICATIONS AND USAGE
Edema
Furosemide tablets are indicated in adults and pediatric patients for the treatment of edema associated with heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Furosemide tablets are particularly useful when an agent with a greater diuretic potential is desired.

Hypertension
Oral furosemide may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with furosemide alone.

CONTRAINDICATIONS
Furosemide tablets are contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide.

WARNINGS
In patients with hepatic cirrhosis and ascites, furosemide therapy has been initiated in the hospital. In patients with hepatic cirrhosis, stated indication for therapy should not be instituted until the basic condition is improved. Sudden alterations of fluid and electrolyte balance in cirrhotics with cirrhosis may precipitate hepatic encephalopathy. Information 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 anemia and oliguria occur during treatment of severe renal disease, furosemide should be discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility
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 at 1.75 times the maximum human dose of 600 mg. There was marginal increases in uncommon tumors in male rats at a dose of 15 mg (slightly greater than the maximum human dose) but not at 30 mg.

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. In mammalian in vivo assays for chromosomal aberrations in mouse bone marrow, no increase in the number of chromatid or sister chromatid exchanges was noted. The drug tested was not mutagenic in bacteria or mammalian cells in vitro in the Salmonella/mammalian microsome test. The results of these tests do not indicate the genotoxic potential of furosemide. The results of studies on the induction of chromosomal aberrations or gene mutations in mammalian cells in vitro have not been reported. The use 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 maximum human dose of 600 mg/day).

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 doses were studied in mice, rats and rabbits.

Furosemide caused uniphasal maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (4 times the maximal recommended human dose of 40 mg/kg). In another study, a dose of 50 mg/kg (4 times the maximal recommended human dose of 40 mg/kg) 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 (dilation 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 nephreotoxicity/rhabdomyolysis. Nephrotoxicity/rhabdomyolysis 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

Clinical and studies of furosemide did not include sufficient subjects of 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 lower 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 (see PRECAUTIONS; General and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

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

Gastrointestinal System Reactions

1. hepatic encephalopathy in patients with hepaticcellular insufficiency
2. pancreatitis
3. jaundice (intrahepatic cholestatic jaundice)
4. increased liver enzymes
5. anemia
6. oral and gastric irritation
7. cramping
8. diaphoresis
9. constipation
10. nausea
11. vomiting

Systemic Hypersensitivity Reactions

1. severe anaphylactic or anaphylactoid reactions (e.g., with shock)
2. allergic circumoral edema
3. interstitial nephritis
4. necrotizing angiitis

Central Nervous System Reactions

1. tremor and hearing loss
2. paresthesias
3. vertigo
4. dizziness
5. headache
6. blurred vision
7. xantheasma

Hematologic Reactions

1. aplastic anemia
2. thrombocytopenia
3. agranulocytosis
4. hemolytic anemia
5. leukopenia
6. anemia
7. eosinophilia

Dermatologic-Hypersensitivity Reactions

1. toxic epidermal necrolysis
2. Stevens-Johnson Syndrome
3. erythema multiforme
4. drug rash with eosinophilia and systemic symptoms
5. acute generalized exanthematous pustulosis
6. urticarial dermatitis
7. bullous pemphigoid
8. purpura
9. photosensitivity
10. rash
11. pruritus
12. urticaria

Cardiovascular Reaction

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

Other Reactions

1. hyperglycemia
2. glycineuria
3. hyperuricemia
4. muscle spasm
5. weakness
6. restlessness
7. urinary bladder spasm
8. thrombophlebitis
9. fever

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

OVERDOSAGE

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 LD50 exceeded 1000 mg/kg body weight, while the intravenous LD50 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 overdose 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).

Intravenous use does not accelerate furosemide elimination.

DOSAGE AND ADMINISTRATION

Edema

Therapy should be individualized according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response.

Adults:
The usual initial dose of furosemide tablets is 20 to 80 mg given as a single dose. Ordinarily a prompt diuresis ensues. If needed, the same dose can be administered 6 to 8 hours later or the dose may be increased. The dose may be raised by 20 or 40 mg and given not sooner than 6 to 8 hours after the previous dose. Doses greater than 20 mg/kg body weight are not recommended. For maintenance therapy in pediatric patients, the dose should be adjusted to the minimum effective level.

Hypertension

Therapy should be individualized according to the patient's response to gain maximal therapeutic response and to determine the minimal dose needed to maintain the therapeutic response.

Adults:
The usual initial dose of furosemide tablets for hypertension is 10 mg, usually divided into 4 to 5 mg twice a day. Dosage should then be adjusted according to response. If response is not satisfactory, other antihypertensive agents may be necessary.

Changes in blood pressure must be carefully monitored when furosemide tablets are used with other antihypertensive drugs, especially during initial therapy. To prevent excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50 percent when furosemide tablets are added to the regimen. As the blood pressure falls under the potentiating effect of furosemide tablets, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

Pediatric Patients:

In general, dose selection and dose adjustment for the elderly patient should be cautious, usually starting at the lower end of the dosing range (see PRECAUTIONS; Geriatric Use).

HOW SUPPLIED

Furosemide Tablets, USP

20 mg: White-off white, oval, debossed “1307” on one side and debossed “V” on the reverse side, available as follows:

- Bottles of 10: ND C 0603-3739-10
- Bottles of 100: ND C 0603-3739-21
- Bottles of 500: ND C 0603-3739-32
- Bottles of 5000: ND C 0603-3739-34

40 mg: White-off white, round, scored, debossed “3170” over “V” on one side and plain on the reverse side, available as follows:

- Bottles of 10: ND C 0603-3740-10
- Bottles of 100: ND C 0603-3740-21
- Bottles of 1000: ND C 0603-3740-32
- Bottles of 5000: ND C 0603-3740-44

80 mg: White-off white, round, scored, debossed “3171” over “V” on one side and plain on the reverse side, available as follows:

- Bottles of 10: ND C 0603-3741-10
- Bottles of 90: ND C 0603-3741-22
- Bottles of 100: ND C 0603-3741-24
- Bottles of 500: ND C 0603-3741-28
- Bottles of 1000: ND C 0603-3741-32

STORAGE

Store at 20° to 25° C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light.

Dispense in well-closed, light-resistant containers. Exposure to light might cause a slight discoloration. Discolored tablets should not be dispensed.

Manufactured for:

QUALITEST PHARMACEUTICALS

Huntsville, AL 35811

R180952

Rev 5/12

R9