CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-241

PRINTED LABELING

FUROSEMIDE

Injection, USP

(10 mg/mL)

Ampul

Fliptop Vial

Ansyr™ Plastic Syringe

Abboject® - PA

Abboject® - Unit of Use Syringe

***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.)

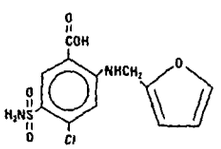
58-0755-R2-Rev. May, 1999

DESCRIPTION

Furosemide Injection, USP is a sterile solution intended for intramuscular or intravenous administration. Each mL contains furosemide 10 mg and sodium chloride sufficient to render solution isotonic in water for injection. Contains sodium hydroxide and may contain hydrochloric acid for pH adjustment. pH 9.0 (8.0 to 9.3).

Furosemide is a diuretic which is an anthranilic acid derivative, chemically identified as 4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid.

Furosemide is a white to off-white odorless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids. It has the following structural formula:



Molecular formula: $C_{12}H_{11}ClN_2O_5S$
Molecular weight: 330.75

The plastic syringe is molded from a specially formulated polypropylene. Water permeates from inside the container at an extremely slow rate which will have an insignificant effect on solution concentration over the expected shelf life.

Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.

Contains no preservative.

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 humans and experimental animals.

It has been demonstrated that furosemide inhibits primarily the reabsorption 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 this unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone.

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

The onset of diuresis following intravenous administration is within 5 minutes and somewhat later after intramuscular administration. The peak effect occurs within the first half hour. The duration of diuretic effect is approximately 2 hours.

route. Parenteral use should be replaced with oral furosemide as soon as practical.

CONTRAINDICATIONS

Furosemide Injection is 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 is best initiated in the hospital. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

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

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

Pediatric Use: In premature neonates with respiratory distress syndrome,

diuretic treatment with furosemide in the first few weeks of life may increase the risk of persistent patent ductus arteriosus (PDA), possibly through a prostaglandin-E-mediated process.

Literature reports indicate that premature infants with post conceptual age (gestational plus postnatal) less than 31 weeks receiving doses exceeding 1 mg/kg/24 hours may develop plasma levels which could be associated with potential toxic effects including ototoxicity.

Hearing loss in neonates has been associated with the use of furosemide injection (see **WARNINGS**, above).

PRECAUTIONS

General

Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients. As with any effective diuretic, electrolyte depletion may occur during furosemide therapy, especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop with furosemide, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

All patients receiving furosemide therapy should be observed for these signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia,

arrhythmia, or gastrointestinal disturbances such as nausea and vomiting.

Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2-hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated.

Patients allergic to sulfonamides may also be allergic to furosemide.

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

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

Information for Patients

Patients receiving furosemide should be advised that they may experience symptoms from excessive fluid and/or electrolyte losses. The postural hypotension that sometimes occurs can usually be managed by getting up slowly. Potassium supplements and/or dietary measures may be needed to control or avoid hypokalemia.

Patients with diabetes mellitus should be told that furosemide may increase blood glucose levels and thereby affect urine glucose tests. The skin of some patients may be more sensitive to the effects of sunlight while taking furosemide.

Hypertensive patients should avoid medications that may increase blood pressure, including over-the-counter products for appetite suppression and cold symptoms.

Laboratory Tests

Serum electrolytes (particularly potassium), CO_2, creatinine and BUN should be determined frequently during the first few months of furosemide therapy and periodically thereafter.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting profusely or receiving parenteral fluids. Abnormalities should be corrected or the drug temporarily withdrawn. Other medications may also influence serum electrolytes.

Reversible elevations of BUN may occur and are associated with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Urine and blood glucose should be checked periodically in diabetics receiving furosemide, even in those suspected of latent diabetes.

Furosemide may lower serum levels of calcium (rarely cases of tetany have been reported) and magnesium. Accordingly, serum levels of these electrolytes should be determined periodically.

Drug Interactions

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

Furosemide should not be used concomitantly with ethacrynic acid because of the possibility of ototoxicity.

Patients receiving high doses of salicylates concomitantly with furosemide, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

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

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

Furosemide may add to or potentiate the therapeutic effect of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

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

One study in six subjects demonstrated that the combination of furosemide and acetylsalicylic acid temporarily reduced creatinine clearance in patients with chronic renal insufficiency. There are case reports of patients who developed increased BUN, serum creatinine and serum potassium levels, and weight gain when furosemide was used in conjunction with NSAIDs.

Literature reports indicate that coadministration 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.

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 17.5 times the

maximum human dose of 600 mg. There were marginal increases in uncommon tumors in male rats at a dose of 15 mg/kg (slightly greater than the maximum human dose) but not at 30 mg/kg.

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

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

Pregnancy

Teratogenic Effects: 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 oral 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.

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

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

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

Nursing Mothers

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

Pediatric Use

Renal calcifications (from barely visible on x-ray to staghorn) have occur in some severely premature infants treated with intravenous furosemide edema due to patent ductus arteriosus and hyaline membrane disease. T concurrent use of chlorothiazide has been reported to decrea hypercalciuria and dissolve some calculi.

ADVERSE REACTIONS

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

Gastrointestinal System Reactions

(1) Pancreatitis (2) jaundice (intrahepatic cholestatic jaundice) (3) anorexia (4) oral and gastric irritation (5) cramping (6) diarrhea (7) constipation (8) nausea (9) vomiting.

Systemic Hypersensitivity Reactions

(1) Systemic vasculitis (2) interstitial nephritis (3) necrotizing angiitis.

Central Nervous System Reactions

(1) Tinnitus and hearing loss (2) paresthesias (3) vertigo (4) dizziness (5) headache (6) blurred vision (7) xanthopsia.

Hematologic Reactions

(1) Aplastic anemia (rare) (2) thrombocytopenia (3) agranulocytosis (rare) (4) hemolytic anemia (5) leukopenia (6) anemia.

Dermatologic-Hypersensitivity Reactions

(1) Exfoliative dermatitis (2) erythema multiforme (3) purpura (4) photosensitivity (5) urticaria (6) rash (7) pruritus.

Cardiovascular Reaction

Orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics.

Other Reactions

(1) Hyperglycemia (2) glycosuria (3) hyperuricemia (4) muscle spasm (5) weakness (6) restlessness (7) urinary bladder spasm (8) thrombophlebitis (9) transient injection site pain following intramuscular injection (10) 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 LD_{50} exceeded 1000 mg/kg body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats.

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

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

Hemodialysis does not accelerate furosemide elimination.

DOSAGE AND ADMINISTRATION

Adults

Parenteral therapy with Furosemide Injection, USP should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical.

Edema

The usual initial dose of furosemide is 20 to 40 mg given as a single dose injected intramuscularly or intravenously. The intravenous dose should be given slowly (1 to 2 minutes). Ordinarily a prompt diuresis ensues. If needed, another dose may be administered in the same manner 2 hours later or the dose may be increased. The dose may be raised by 20 mg and given not sooner than 2 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily.

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

If the physician elects to use high dose parenteral therapy, add the Furosemide Injection to either Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, or Dextrose (5%) Injection, USP after pH has been adjusted to above 5.5, and administer as a controlled intravenous infusion at a rate not greater than 4 mg/min. Furosemide Injection is a buffered alkaline solution with a pH of about 9 and drug may precipitate at pH values below 7. Care must be taken to ensure that the pH of the prepared infusion solution is in the weakly alkaline to neutral range. Acid solutions, including other parenteral medications (e.g., labetalol, ciprofloxacin, amrinone, milrinone) must not be administered concurrently in the same infusion because they may cause precipitation of the furosemide. In addition, furosemide injection should not be added to a running intravenous line containing any of these acidic products.

Acute Pulmonary Edema

The usual initial dose of furosemide is 40 mg injected slowly intravenously (over 1 to 2 minutes). If a satisfactory response does not occur within 1 hour, the dose may be increased to 80 mg injected slowly intravenously (over 1 to 2 minutes).

If necessary, additional therapy (e.g., digitalis, oxygen) may be administered concomitantly.

Pediatric Patients

Parenteral therapy should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical.

The usual initial dose of Furosemide (intravenously or intramuscularly) in pediatric patients is 1 mg/kg body weight and should be given slowly under close medical supervision. If the diuretic response to the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. Doses greater than 6 mg/kg body weight are not recommended.

Literature reports suggest that the maximum dose for premature infants should not exceed 1 mg/kg/day (see **WARNINGS, Pediatric Use**).

Furosemide Injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored.

To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand.

HOW SUPPLIED

Furosemide Injection, USP 10 mg/mL is supplied as follows:

List No.	Container	Size
6101	Amber Ampul	2 mL
6101 —	Amber Ampul	4 mL
6101 —	Amber Ampul	10 mL
1639	Ansyr™ Plastic Syringe	10 mL
9631	Ansyr™ Plastic Syringe	4 mL
6054	Abboject®—PA Unit of Use Syringe	2 mL
6055	Abboject—Unit of Use Syringe	4 mL
6056 —	Abboject—Unit of Use Syringe	10 mL
6056 —	Abboject—Unit of Use Syringe	8 mL
6102	Amber Fliptop Vial	2 mL
6102 —	Amber Fliptop Vial	4 mL
6102 —	Amber Fliptop Vial	10 mL

Store at controlled room temperature 15° to 30°C (59° to 86°F).
Do not use if solution is discolored or contains particulate.
Protect from light. Do not remove from carton until ready for use.
Discard unused portion.

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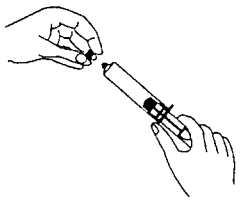
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

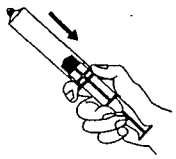

10
20
30
40
4 mL Single-dose
NDC 0074-9631-04
FUROSEMIDE Injection, USP
40 mg (10 mg/mL)
For I.V. or I.M. use. Sterile, nonpyrogenic. Do not use if solution is discolored or contains particulate. Contains no preservative.
Abbott Laboratories, North Chicago, IL 60064, USA
MAY 28

USE ASEPTIC TECHNIQUE

1. Remove luer cover.



2. Pull the barrel down until air is expelled from the syringe.



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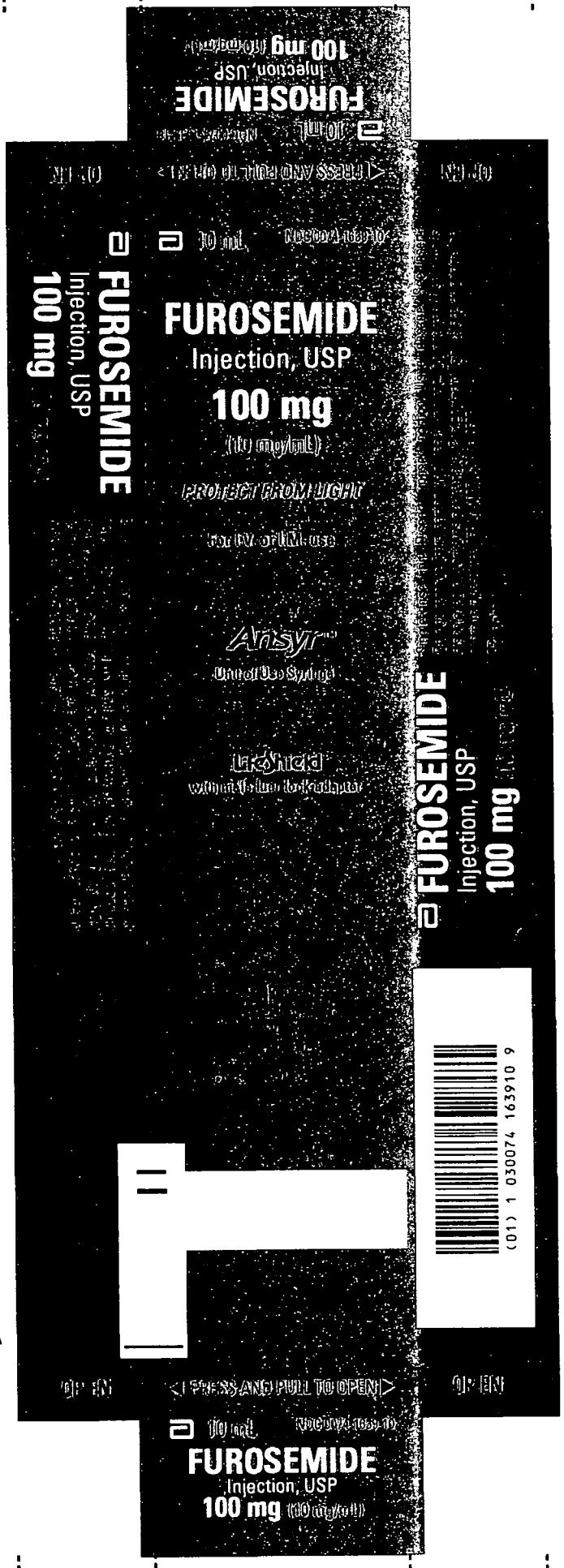

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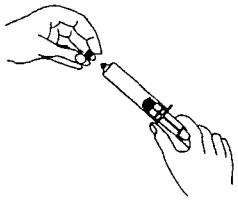

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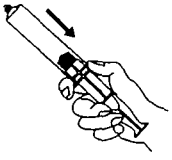

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Injection, USP
40 mg

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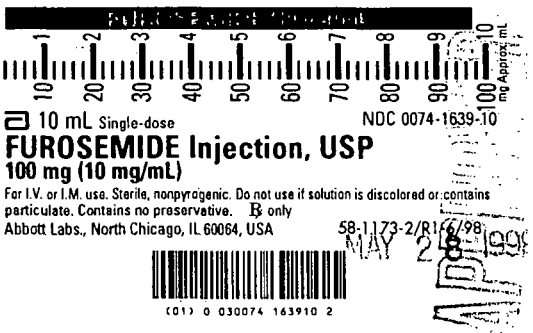
10 20 30 40 50 60 70 80 90 100
mg Approx. mL
10 mL Single-dose
NDC 0074-1639-10
FUROSEMIDE Injection, USP
100 mg (10 mg/mL)
For I.V. or I.M. use. Sterile, nonpyrogenic. Do not use if solution is discolored or contains particulate. Contains no preservative. ℞ only
Abbott Labs., North Chicago, IL 60064, USA
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