HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FUROSCIX safely and effectively. See full prescribing information for FUROSCIX.

FUROSCIX® (furosemide injection), for subcutaneous use
Initial U.S. Approval: 1968

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	12/2025
Dosage and Administration (2)	7/2026
Warnings and Precautions, Incomplete Dosing (5.5)	7/2026

----------INDICATIONS AND USAGE----------
FUROSCIX is a loop diuretic indicated for the treatment of edema in pediatric patients weighing 43 kg and above and in adult patients with chronic heart failure or chronic kidney disease, including the nephrotic syndrome. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- FUROSCIX is not for chronic use and should be replaced with oral diuretics as soon as practical. (2.1)
- The FUROSCIX ReadyFlow™ is pre-filled to deliver 80 mg of furosemide subcutaneously in about 10 seconds.
- The single-use, On-body Infusor is pre-programmed to deliver 30 mg of furosemide subcutaneously over the first hour then 12.5 mg per hour for the subsequent 4 hours. (2.1)
- See Full Prescribing Information for important administration instructions. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection:
- 80 mg/mL in a single-dose prefilled autoinjector (3)
- 80 mg/10 mL (8 mg/mL) in a single-dose prefilled cartridge co-packaged with a single-use On-body Infusor (3)

----------CONTRAINDICATIONS----------
- Anuria (4)
- Hypersensitivity to furosemide, or components of FUROSCIX formulation (4)
- FUROSCIX On-body Infusor: Hypersensitivity to medical adhesives (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Fluid, Electrolyte, and Metabolic Abnormalities: Monitor serum electrolytes, CO_2, BUN, creatinine, glucose, and uric acid. (5.1)
- Worsening Renal Function: Monitor for dehydration and azotemia. (5.2)
- Ototoxicity: Avoid higher than recommended doses. (5.3, 7.1)
- Acute Urinary Retention: Monitor patients with symptoms of urinary retention. (5.4)
- Incomplete Dosing: Fluid contact and certain patient movements during treatment may cause the On-body Infusor to prematurely terminate infusion. Ensure the patient or caregiver can detect and respond to alarms. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions during treatment with FUROSCIX were administration site and skin reactions: erythema, bruising, edema and pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact MannKind Corporation at 1-877-323-8505 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Aminoglycoside antibiotics: Increased potential ototoxicity of the antibiotics. Avoid combination. (7.1)
- Ethacrynic acid: Risk of ototoxicity. Avoid combination (7.1)
- Salicylates: Risk of salicylate toxicity. (7.1)
- Cisplatin and nephrotoxic drugs: Risk of ototoxicity and nephrotoxicity. (7.1)
- Lithium: Risk of lithium toxicity. (7.1)
- Renin-angiotensin inhibitors: Increased risk of hypotension and renal failure. (7.1)
- Adrenergic blocking drugs: Risk of potentiation. (7.1)
- Drugs undergoing renal tubular secretion: Risk of toxicity potentiation. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised 7/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FUROSCIX is indicated for the treatment of edema in pediatric patients weighing 43 kg and above and in adult patients with chronic heart failure or chronic kidney disease (CKD), including the nephrotic syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

FUROSCIX is not for chronic use and should be replaced with oral diuretics as soon as practical.

Adult Patients: FUROSCIX ReadyFlow: The FUROSCIX ReadyFlow is an autoinjector that delivers 80 mg of furosemide subcutaneously in about 10 seconds *[see Clinical Pharmacology (12)]*.

Adult and Pediatric Patients 43 kg and Above: On-body Infusor for FUROSCIX: The single-use, On-body Infusor with prefilled cartridge is pre-programmed to deliver 30 mg of furosemide subcutaneously over the first hour followed by 12.5 mg per hour for the subsequent 4 hours *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12)]*.

2.2 Important Administration Instructions

Inspect the parenteral drug product through the autoinjector viewing window or the prefilled cartridge for the On-body Infusor prior to administration. FUROSCIX is a clear, colorless to slightly yellow solution. Do not use FUROSCIX if you see particles or the solution is discolored or cloudy *[see Description (11)]*.

FUROSCIX is intended for administration to the abdomen only. For each subcutaneous administration, rotate the site on the abdomen.

Refer to the Instructions for Use for additional information.

FUROSCIX ReadyFlow (Adult Patients):

Instruct patients to select and clean an injection site on the abdomen at least two inches away from the belly button (navel) and avoid skin that is irritated or broken and areas with scars or stretch marks. Pull the blue cap straight off the FUROSCIX ReadyFlow and then firmly push and hold against the skin until the yellow plunger rod stops moving and fills the viewing window, about 10 seconds.

On-body Infusor for FUROSCIX (Adult and Pediatric Patients 43 kg and above):

The On-body Infusor for FUROSCIX is not compatible with use in an MRI setting.

The On-body Infusor for FUROSCIX is intended for use in a setting where the patient can limit their activity for the duration of administration *[see Warnings and Precautions (5.5)]*.

Load the prefilled cartridge of furosemide into the On-body Infusor and close the cartridge holder.

Peel away the adhesive liner on the On-body Infusor and apply onto a clean, dry area of the abdomen between the top of the beltline and the bottom of the ribcage that is not tender, bruised, red or indurated. The distance from the top of the beltline to the bottom of the ribcage should be at least 2 ½ inches.

Start the injection by firmly pressing and releasing the blue start button.

Do not remove until the injection is complete (signaled by the solid green status light, beeping sound, and the white plunger rod filling the cartridge window).

In pediatric patients weighing at least 43 kg, FUROSCIX On-body Infusor must be administered by a healthcare provider or adult caregiver. Adult patients or caregivers should receive proper instruction in preparing and administering FUROSCIX before using the FUROSCIX On-body Infusor.

3 DOSAGE FORMS AND STRENGTHS

Injection:

- 80 mg/mL as a clear, colorless to slightly yellow solution in a single-dose prefilled autoinjector.
- 80 mg/10 mL (8 mg/mL) as a clear to slightly yellow solution in a single-dose prefilled cartridge for use only with co-packaged single-use, On-body Infusor.

4 CONTRAINDICATIONS

FUROSCIX is contraindicated in:

- Patients with anuria.
- Patients with a history of hypersensitivity to furosemide, or any component of the FUROSCIX formulation.
- The On-body Infusor for FUROSCIX is contraindicated in patients with a history of hypersensitivity to medical adhesives

5 WARNINGS AND PRECAUTIONS

5.1 Fluid, Electrolyte, and Metabolic Abnormalities

Furosemide may cause fluid, electrolyte, and metabolic abnormalities such as hypovolemia, hypokalemia, azotemia, hyponatremia, hypochloremic alkalosis, hypomagnesemia, hypocalcemia, hyperglycemia, or hyperuricemia, particularly in patients receiving higher doses, patients with inadequate oral electrolyte intake, and in elderly patients. Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients. Serum electrolytes, CO_2, BUN, creatinine, glucose, and uric acid should be monitored frequently during furosemide therapy *[see Use in Specific Populations (8.6)]*.

5.2 Worsening Renal Function

Furosemide can cause dehydration and azotemia. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, discontinue furosemide *[see Clinical Pharmacology (12.3)]*.

5.3 Ototoxicity

Cases of tinnitus and reversible or irreversible hearing impairment and deafness have been reported with furosemide. Reports usually indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, the use of higher than recommended doses, hypoproteinemia 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) *[see Drug Interactions (7.1)]*.

5.4 Acute Urinary Retention

In patients with severe symptoms of urinary retention (because of bladder emptying disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine. These patients require careful monitoring, especially during the initial stages of treatment.

5.5 Incomplete Dosing

The FUROSCIX ReadyFlow should be held against the abdomen until the yellow plunger rod stops moving and fills the viewing window. This may take about 10 seconds.

The On-body Infusor for FUROSCIX should not be allowed to get wet from water or any other fluids (blood or drug product). Fluid contact with the circuit board can lead to device errors and premature termination of infusion.

The On-body Infusor for FUROSCIX is intended for use in a setting where the patient can limit their activity for the duration of administration. Certain patient movements may cause interruption of device adherence to skin and premature termination of infusion.

The On-body Infusor for FUROSCIX should only be administered in settings where alarms can be detected and responded to in order to ensure a complete dose is administered *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are discussed elsewhere in the labeling:

- Fluid, Electrolyte, and Metabolic Abnormalities *[see Warnings and Precautions (5.1)]*
- Ototoxicity *[see Warnings and Precautions (5.3)]*

The following adverse reactions associated with the use of furosemide were identified in clinical trials or post-marketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably, or to establish a causal relationship to drug exposure.

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

Gastrointestinal System Reactions: pancreatitis, jaundice (intrahepatic cholestatic jaundice), increased liver enzymes, anorexia, oral and gastric irritation, cramping, diarrhea, constipation, nausea, vomiting.

Systemic Hypersensitivity Reactions: severe anaphylactic or anaphylactoid reactions (e.g., with shock), systemic vasculitis, interstitial nephritis, necrotizing angiitis.

Central Nervous System Reactions: tinnitus and hearing loss, paresthesias, vertigo, dizziness, headache, blurred vision, xanthopsia.

Hematologic Reactions: aplastic anemia, thrombocytopenia, agranulocytosis, hemolytic anemia, leukopenia, anemia, eosinophilia.

Dermatologic Hypersensitivity Reactions: toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, drug rash with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, exfoliative dermatitis, bullous pemphigoid, purpura, photosensitivity, rash.

Cardiovascular Reactions: orthostatic hypotension, increase in cholesterol and triglyceride serum levels.

Administration Site and Skin Reactions: administration site erythema, bruising, edema, mass, pruritus, and pain.

Other Reactions: glycosuria, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis, transient injection site pain following intramuscular injection, fever.

7 DRUG INTERACTIONS

7.1 Effects of Furosemide on Other Drugs

Drug/Substance Class or Name	**Drug Interaction Effect**	**Recommendations**
Aminoglycoside antibiotics	Furosemide may increase the ototoxic potential of aminoglycoside antibiotics, especially in the presence of impaired renal function *[see Warnings and Precautions (5.3)]*.	Avoid combination except in life-threatening situations.
Ethacrynic acid	Possibility of ototoxicity *[see Warnings and Precautions (5.3)]*.	Avoid concomitant use with ethacrynic acid.
Salicylates	May experience salicylate toxicity at lower doses because of competitive renal excretory sites.	Monitor for symptoms of salicylate toxicity.
Cisplatin	There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly *[see Warnings and Precautions (5.3)]*.	Administer furosemide at lower doses and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment. Monitor renal function.
Cisplatin and nephrotoxic drugs	Nephrotoxicity	
Paralytic agents	Furosemide has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.	Monitor for skeletal muscle effect.
Lithium	Furosemide reduces lithium's renal clearance and add a high-risk of lithium toxicity.	Avoid concomitant use with lithium.

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers	May lead to severe hypotension and deterioration in renal function, including renal failure.	Monitor for changes in blood pressure and renal function and interrupt or reduce the dosage of furosemide, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers if needed.
Antihypertensive drugs	Furosemide may add to or potentiate the therapeutic effect of other antihypertensive drugs.	Monitor for changes in blood pressure and adjust the dose of other antihypertensive drugs if needed.
Adrenergic blocking drugs or peripheral adrenergic blocking drugs	Potentiation occurs.	Monitor for changes in blood pressure and adjust the dose of adrenergic blocking drugs if needed.
Norepinephrine	Furosemide may decrease arterial responsiveness (vasoconstricting effect) to norepinephrine.	Monitor blood pressure (or mean arterial pressure).
Chloral hydrate	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.	Concomitant use with chloral hydrate is not recommended.
Methotrexate and other drugs undergoing renal tubular secretion	Furosemide may decrease renal elimination of other drugs that undergo tubular secretion. High-dose treatment of furosemide may result in elevated serum levels of these drugs and may potentiate their toxicity.	Monitor serum levels of drugs undergoing renal tubular secretion and adjust the dose if needed.
Cephalosporin	Furosemide can increase the risk of cephalosporin-induced nephrotoxicity even in the setting of minor or transient renal impairment.	Monitor for changes in renal function.

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Cyclosporine	Increased risk of gouty arthritis secondary to furosemide-induced hyperuricemia and cyclosporine impairment of renal urate excretion.	Monitor serum urate levels.
Thyroid hormones	High-doses (> 80 mg) of furosemide may inhibit the binding of thyroid hormones to carrier proteins and result in transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels.	Monitor the total thyroid hormone levels.

7.2 Effect of Other Drugs on Furosemide

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Phenytoin	Phenytoin interferes directly with renal action of furosemide.	Monitor diuretic effects of furosemide and adjust the dose of furosemide if needed.
Methotrexate and other drugs undergoing renal tubular secretion	May reduce the effect of furosemide. High-dose treatment of methotrexate and these other drugs may result in elevated serum levels of furosemide and may potentiate the toxicity of furosemide.	Monitor for enhanced toxicity of furosemide.
Indomethacin	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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published observational studies, case reports, and post marketing reports, from decades of use, have not demonstrated a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes with furosemide use during pregnancy. Untreated congestive heart failure and cirrhosis of the liver can lead to adverse outcomes for the mother and the fetus (*see Clinical Considerations*).

In animal reproduction studies, furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits when administered orally during organogenesis at 4 times a human i.v. dose of 80 mg based on body surface area (BSA) and oral bioavailability corrections, presumably secondary to volume depletion (*see Data*).

FUROSCIX ReadyFlow contains benzyl alcohol (BA) as a preservative. Because BA is rapidly metabolized by a pregnant female, BA exposure in the fetus is unlikely. The estimated background risk for major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/fetal Risk

Pregnant women with congestive heart failure are at increased risk for pre-term birth. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Clinical classification of heart disease may worsen with pregnancy and lead to maternal death and/or stillbirth. Closely monitor pregnant patients for destabilization of their heart failure.

Pregnant women with symptomatic cirrhosis generally have poor outcomes including hepatic failure, variceal hemorrhage, pre-term delivery, fetal growth restriction and maternal death. Outcomes are worse with coexisting esophageal varices. Carefully monitor pregnant women with cirrhosis of the liver.

Data

Animal Data

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

Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (approximately 4 times the human i.v. dose of 80 mg based on BSA and oral bioavailability corrections). In another study, a dose of 50 mg/kg (approximately 7 times a human i.v. dose of 80 mg based on BSA and oral bioavailability corrections) 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 an oral 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 (distention of the renal pelvis and, in some cases, of the ureters) in fetuses of treated dams as compared with the incidence of fetuses from the control group.

8.2 Lactation

Risk Summary

The presence of furosemide has been reported in human breast milk. There are no data on the effects on the breastfed infant or the effects on milk production. Doses of furosemide associated with clinically significant diuresis may impair milk production. FUROSCIX ReadyFlow contains benzyl alcohol (BA) as a preservative. Because BA is rapidly metabolized by a pregnant female, BA exposure in the breastfed neonate is unlikely. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for furosemide and any potential adverse effects on the breastfed infant from furosemide or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of the FUROSCIX ReadyFlow for pediatric use have not been established.

The On-body Infusor for FUROSCIX is approved for the treatment of edema in pediatric patients weighing at least 43 kg with chronic heart failure or chronic kidney disease, including the nephrotic syndrome. FUROSCIX has not been studied in pediatric patients. Use of FUROSCIX for this indication is supported by: 1) efficacy, safety, and pharmacokinetic data of furosemide in adult and pediatric patients; 2) pharmacokinetic and pharmacodynamic data of FUROSCIX in adults with New York Heart Association (NYHA) Functional Classification Class II and Class III heart failure *[see Clinical Pharmacology (12.2, 12.3)]*; and 3) population pharmacokinetic modeling which demonstrated no significant difference in furosemide exposure following FUROSCIX administration in a simulated pediatric population weighing 43 kg and above and aged 6 to <17 years compared to adult patients with chronic heart failure *[see Clinical Pharmacology (12.3)]*.

FUROSCIX is not approved for the treatment of edema in pediatric patients weighing less than 43 kg.

8.5 Geriatric Use

Controlled clinical studies did not include sufficient numbers of subjects to determine whether subjects aged 65 and over 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 patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

FUROSCIX 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 Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Significantly reduced renal function can affect the response to furosemide. The FUROSCIX ReadyFlow and the On-body Infusor will deliver only an 80 mg dose of furosemide, and patients with significantly reduced renal function may require additional diuretic therapy.

8.7 Hepatic Impairment

In patients with hepatic cirrhosis and ascites, sudden alterations of fluid and electrolyte balance may precipitate hepatic encephalopathy and coma. Treat such patients in a setting where clinical status and electrolyte balance can be carefully monitored.

10 OVERDOSAGE

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

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).

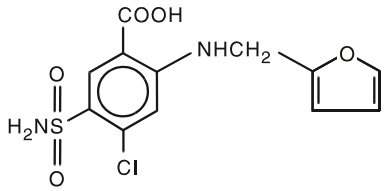
Hemodialysis does not accelerate furosemide elimination.

11 DESCRIPTION

FUROSCIX (furosemide injection, 80 mg/10 mL or 80 mg/mL) is a loop diuretic which is an anthranilic acid derivative.

Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

Furosemide is a white to slightly yellow crystalline powder. It is sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids. The structural formula is as follows:



Molecular Formula:	Molecular Weight:
$C_{12}H_{11}ClN_2O_5S$	330.75 g/mol

FUROSCIX ReadyFlow:

The ReadyFlow is a disposable, fixed single-dose, mechanical spring driven autoinjector. The ReadyFlow is preloaded with the prefilled syringe containing the drug and delivers 80 mg of furosemide in about 10 seconds.

The single-dose prefilled FUROSCIX ReadyFlow contains 80 mg per 1 mL sterile, clear, colorless to slightly yellow, and non-pyrogenic furosemide solution. The pH of FUROSCIX for administration via the ReadyFlow, 7.7, differs from that of Furosemide Injection, USP.

Autoinjector contains 1 mL of FUROSCIX ReadyFlow that contains 80 mg furosemide and the following inactive ingredients: benzyl alcohol (35 mg), hydrochloric acid for pH adjustment if needed, sodium hydroxide for pH adjustment if needed, tromethamine (9.7 mg), and water for injection (q.s.).

On-body Infusor for FUROSCIX:

The On-body Infusor for FUROSCIX is a wearable, single-use, electromechanical (battery powered, micro-processor controlled), on-body delivery system that is pre-programmed to deliver 80 mg of furosemide over 5-hours using a bi-phasic delivery profile.

FUROSCIX for administration via the On-body Infusor is provided in a single-dose prefilled cartridge co-packaged with a single-use, On-body Infusor. The single-dose prefilled cartridge contains 80 mg per 10 mL sterile, clear, colorless to slightly yellow, and non-pyrogenic furosemide solution. The pH of FUROSCIX for administration via the On-body Infusor, 7.4, differs from that of Furosemide Injection, USP.

Each 1 mL of FUROSCIX for administration via the On-body Infusor contains the following inactive ingredients: hydrochloric acid for pH adjustment if needed, sodium chloride (5.84 mg), sodium hydroxide for pH adjustment if needed, tris HCl (7.88 mg), and water for injection (q.s.).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Furosemide primarily inhibits the reabsorption of sodium and chloride in the proximal and distal tubules and in the loop of Henle. The high degree of diuresis is largely due to the unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone.

12.2 Pharmacodynamics

In healthy adults, subcutaneous administration of FUROSCIX (80 mg furosemide injection via the ReadyFlow) produced similar diuresis, natriuresis, and kaliuresis to intravenous administration (two 40 mg bolus doses separated by 120 minutes) at 6, 8, and 12 hours post-dose. The duration of diuretic effect with FUROSCIX ReadyFlow was up to 6 hours after initiation of dosing.

In adult patients with NYHA Class II and Class III heart failure, subcutaneous administration of FUROSCIX (30 mg furosemide over the first hour followed by 12.5 mg per hour for the subsequent 4 hours, total 80 mg furosemide) produced similar diuresis and natriuresis to intravenous administration (two 40 mg bolus doses separated by 120 minutes) at 8 and 24 hours post-dose. The duration of diuretic effect with FUROSCIX On-body Infusor was up to 8 hours after initiation of dosing.

12.3 Pharmacokinetics

Absorption

In healthy adults, subcutaneous injection of FUROSCIX (80 mg furosemide injection via the ReadyFlow), the bioavailability was 107.3% (90% CI: 103.9, 110.8) relative to 80 mg intravenous furosemide (two 40-mg bolus doses separated by 120 minutes) with a median (min-max) T_{max} of 0.75 (0.5-1.5) hours. The pharmacokinetic parameters of FUROSCIX following subcutaneous injection via the ReadyFlow autoinjector are presented in Table 1 below:

Table 1: Pharmacokinetic Data of FUROSCIX Following Subcutaneous Injection via the ReadyFlow Autoinjector (n = 19)

Dose	C_{max} (ng/mL)	AUC_t (ng×hr/mL)	$T_{1/2}$ (hr)	AUC_∞ (ng×hr/mL)
FUROSCIX: 80 mg injection via the ReadyFlow	4,530 ± 1,500	12,500 ± 4,010	2.2 ± 0.3	12,700 ± 4,120
Furosemide administered as 2 x 40 mg bolus doses intravenously, separated by 120 minutes (total dose: 80 mg furosemide)	10,100 ± 2,810	11,700 ± 3,450	1.9 ± 0.4	11,800 ± 3,510

In adult patients with NYHA Class II-III congestive heart failure, subcutaneous infusion of FUROSCIX (30 mg furosemide over the first hour followed by 12.5 mg per hour for the subsequent 4 hours, 80 mg furosemide total), the bioavailability was 99.6% (90% CI: 94.8, 104.8) relative to 80 mg intravenous furosemide (two 40-mg bolus doses separated by 120 minutes) with a median T_{max} (min-max) of 4 (1.00 - 5.08) hours. The pharmacokinetic parameters of FUROSCIX following subcutaneous infusion via the On-body Infusor are presented in Table 2 below:

Table 2: Pharmacokinetic Data of FUROSCIX Following Subcutaneous Infusion via the On-body Infusor (n = 15)

Dose	C_{max} (ng/mL)	AUC_t (ng×hr/mL)	$T_{1/2}$ (hr)	AUC_∞ (ng×hr/mL)
FUROSCIX: 30 mg subcutaneously infused over the first hour followed by 12.5 mg per hour for the subsequent 4 hours (total dose: 80 mg furosemide)	2,040 ± 449	13,000 ± 4,000	3.2 ± 0.9	13,100 ± 4,010
Furosemide administered as 2 x 40 mg bolus doses intravenously, separated by 120 minutes (total dose: 80 mg furosemide)	8,580 ± 2,540	13,000 ± 4,050	2.6 ± 0.3	13,200 ± 4,170

The impact of subcutaneous edema at the administration site of FUROSCIX on drug absorption is unknown.

Distribution

Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 mcg per mL to 400 mcg per mL are 91% to 99% bound in healthy individuals. The unbound fraction averages 2.3% to 4.1% at therapeutic concentrations.

Elimination

The terminal half-life of furosemide is approximately 2 hours.

Metabolism

Furosemide glucuronide is the only or at least the major biotransformation product of furosemide in humans.

Excretion

Significantly more furosemide is excreted in urine following the intravenous injection than after the tablet or oral solution.

Specific Populations

Pediatric Patients

FUROSCIX was not evaluated in a pediatric clinical study. Based on population pharmacokinetic modeling and simulation, pediatric patients aged 6 to <17 years and weighing 43 kg and above are predicted to have comparable exposures to adult patients following FUROSCIX administration using the FUROSCIX On-body Infusor.

Geriatric Patients

Furosemide binding to albumin may be reduced in elderly patients. Furosemide is predominantly excreted unchanged in the urine.

The renal clearance of furosemide after intravenous administration in older healthy male subjects (60 to 70 years of age) is significantly less 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 subjects *[see Use in Specific Populations (8.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 approximately 8 times a human i.v. dose of 80 mg based on BSA and oral bioavailability corrections. There were marginal increases in uncommon tumors in male rats at a dose of 15 mg per kg (slightly greater than the maximum human dose) but not at 30 mg per kg.

Mutagenesis

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*.

Impairment of Fertility

Furosemide produced no impairment of fertility in male or female rats, at 100 mg per kg per day (the maximum effective diuretic dose in the rat), approximately 7 times a human i.v. dose of 80 mg based on BSA and oral bioavailability corrections.

16 HOW SUPPLIED/STORAGE AND HANDLING

FUROSCIX injection is a sterile, clear, colorless to slightly yellow, non-pyrogenic liquid supplied either in a single-dose autoinjector for subcutaneous injection or in a single-dose prefilled cartridge for subcutaneous infusion co-packaged with the On-body Infusor.

Carton containing one 80 mg/mL single-dose prefilled autoinjector	NDC 71767-111-01
Carton containing one 80 mg/10 mL (8 mg/mL) prefilled cartridge co-packaged with one On-body Infusor	NDC 71767-100-01

Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Do not refrigerate or freeze.

Protect from light. Do not remove the FUROSCIX ReadyFlow or cartridge for use in the On-body Infusor from carton until it is ready for use. Do not use if you see particles in the solution or if the solution is discolored or cloudy. Protect the On-body Infusor for FUROSCIX from water.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling *[see FDA-approved* Instructions for Use*]*.

Advise patients that they should not allow the On-body Infusor to come into contact with water or other fluids. Advise patients and/or caregivers to check the device for alarms to ensure a complete dose is administered *[see Warnings and Precautions (5.5)]*.

Fluid, Electrolyte, and Metabolic Abnormalities

Advise patients 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 *[see Warnings and Precautions (5.1)]*.

Advise patients that furosemide may increase blood glucose levels and thereby affect urine glucose tests *[see Warnings and Precautions (5.1)]*.

Photosensitivity

The skin of some patients may be more sensitive to the effects of sunlight while taking furosemide *[see Adverse Reactions (6)]*.

Advise hypertensive patients to avoid medications that may increase blood pressure, including over-the-counter products for appetite suppression and cold symptoms *[see Drug Interactions (7.1)]*.

For more information about FUROSCIX, go to www.FUROSCIX.com or call 1-877-323-8505

mannkind

FUROSCIX® (furosemide injection) for subcutaneous use

Manufactured for:
MannKind Corporation
25 Mall Road
Burlington, MA 01803
Patent: www.mannkindcorp.com/patent-notices

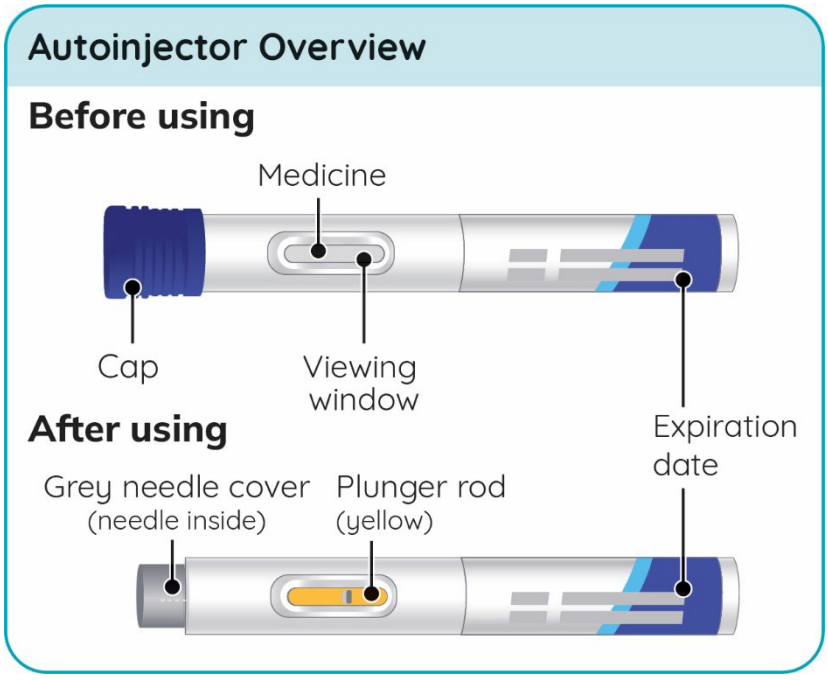
REG-0018 Rev 05

INSTRUCTIONS FOR USE

FUROSCIX ReadyFlow™ [fue roe' six]
(furosemide injection) for subcutaneous use
Single-dose autoinjector
80 mg/mL

This Instructions for Use contains information on how to use the FUROSCIX ReadyFlow autoinjector to inject an 80 mg dose of furosemide under the skin (subcutaneous). Read this Instructions for Use before using the FUROSCIX ReadyFlow autoinjector.

Before using the FUROSCIX ReadyFlow autoinjector, your healthcare provider should show you how to use it the right way. If you have any questions, ask your healthcare provider.



INSTRUCTIONS FOR USE

Important Information You Need to Know Before Using the FUROSCIX ReadyFlow autoinjector

- The autoinjector is for single use only.
- The autoinjector is for subcutaneous (under the skin) injection into the stomach area (abdomen) only.

Before injection

- **Do not** remove the blue Cap until you are ready to inject (see Step 6).
- **Do not** touch or push on the Needle cover. The needle is covered by the grey Needle cover and will not be seen.
- **Do not** use in extreme heat or cold.

During injection

- **Only inject into the stomach area (abdomen)**. **Do not** inject into any other area of the body.
- **Do not** lift the autoinjector from your skin before the yellow Plunger rod has stopped moving and fills the Viewing window.
- If the yellow Plunger rod does not move or does not fill the Viewing window, contact your healthcare provider.
- If you lift the autoinjector too early or do not press the autoinjector firmly against the skin for the entire injection, the Medicine may appear on the skin or squirt from the needle, and you may not get your full dose of FUROSCIX. If you believe you have not received a full dose, contact your healthcare provider.

After injection

- You should notice an **increase in urine production about an hour after the injection** and may need to make frequent bathroom visits. Be sure you have access to a bathroom for up to 6 hours after the injection. If you do not notice the need to use the bathroom, contact your healthcare provider.

Storing FUROSCIX ReadyFlow autoinjector

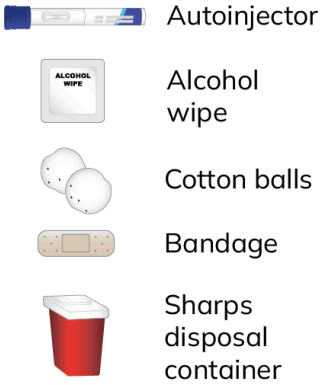
- The autoinjector should be stored at room temperature between 68°F and 77°F (20°C and 25°C).
- **Do not refrigerate or freeze.**
- Keep the autoinjector in the original carton until ready to use to protect from light.
- **Keep the autoinjector and all medicines out of the reach of children.**

Preparing to Inject

1. Gather supplies

Gather all supplies needed for your injection on a clean, well-lit work surface:

- FUROSCIX ReadyFlow autoinjector
- Other supplies (not included)
  - Alcohol wipe
  - Cotton balls or gauze
  - Small bandage
  - Sharps disposal container (see Step 9)

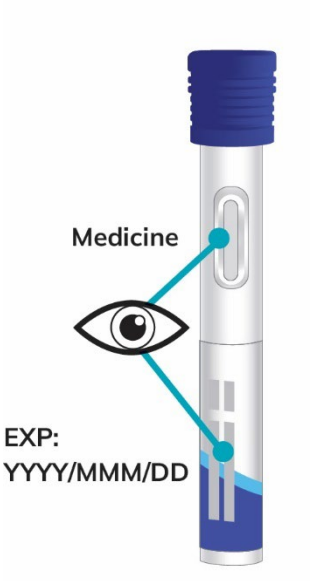


2. Inspect autoinjector

Inspect the autoinjector and make sure:

- the Medicine in the Viewing window is clear and colorless to slightly yellow
- the Expiration date has not passed
- there are no signs of cracks or damage

- **Do not** use the autoinjector if you see particles in the Medicine.
- **Do not** use the autoinjector if the Medicine is discolored or cloudy.
- **Do not** use the autoinjector after the Expiration date.
- **Do not** use the autoinjector if there are signs of cracks or damage.



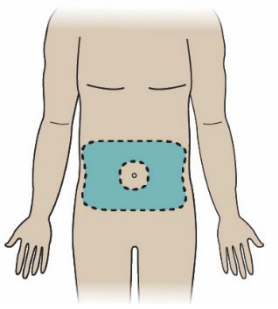
3. Wash hands

Wash your hands with soap and water before using the autoinjector.

4. Select injection site on the stomach area (abdomen)

Select an injection site on the **stomach area only**, at least two inches away from the belly button (navel).

- **Do not** select a site where the skin is irritated or broken. Avoid areas with scars or stretch marks.
- Make sure you switch areas on the stomach area each time you give an injection.

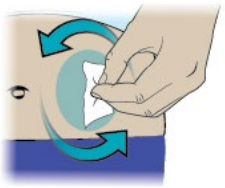


Stomach area (abdomen) only

5. Clean the injection site

Wipe the injection site with an alcohol wipe and allow the area to dry.

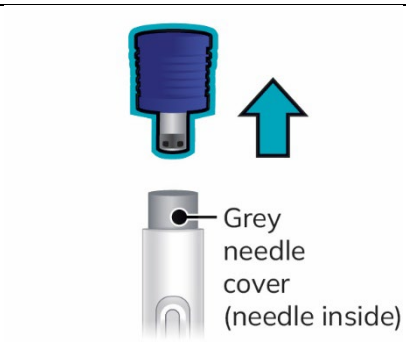
Do not blow on or touch the cleaned area again before injecting.



Injecting FUROSCIX

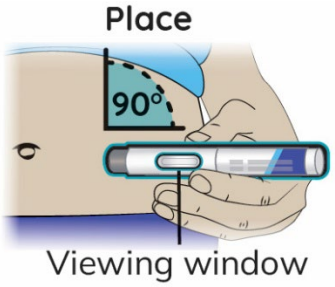
6. Remove Cap

- Pull the blue Cap straight off and throw away (dispose of) Cap.
- When the Cap is removed, use the autoinjector right away.
  - **Do not** put the Cap back onto the autoinjector.
  - **Do not** touch or push on the grey Needle cover (needle inside).



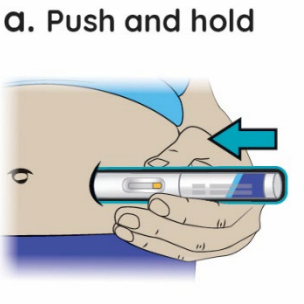
7. Place autoinjector

Hold the autoinjector at 90 degrees with the grey Needle cover flat against the clean stomach area injection site. **Make sure you can see the Viewing window.**

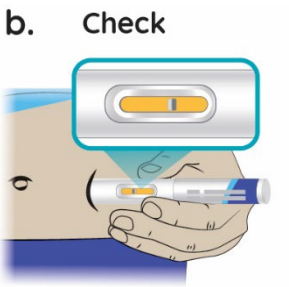


8. Deliver injection

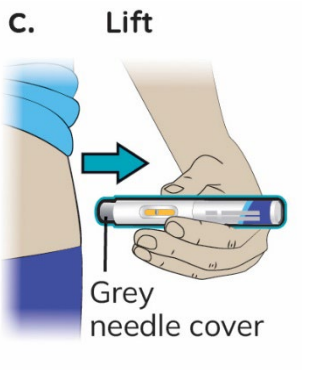
a. **Firmly push and hold the autoinjector** against stomach area until the yellow Plunger rod stops moving. This may take about 10 seconds.
- You may or may not hear 2 clicks during the injection.
- Do not lift the autoinjector while the yellow Plunger rod is moving.
- If the yellow Plunger rod does not start moving, press the autoinjector more firmly against your skin.



b. Check that the yellow Plunger rod has stopped moving and fills the Viewing window.
- **Do not** lift the autoinjector before the injection is done.
- If the Viewing window does not turn completely yellow, or if you see Medicine coming out of the autoinjector, you might not have received a full dose. Contact your healthcare provider.



c. When the injection is complete, lift the autoinjector. The grey Needle cover will automatically extend and lock out over the needle.
- **Do not** reuse the autoinjector. You cannot stop and restart an injection. **It is for single use only.**
- If you see some blood at the injection site, this is normal. Lightly dab with a cotton ball and apply a small bandage.



After Injecting

9. Throw away (dispose of) the autoinjector

Put your used autoinjector into an FDA-cleared sharps disposal container right away after use.

Do not throw away (dispose of) the autoinjector in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that:
- is made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- is upright and stable during use,
- is leak-resistant, and
- is properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

- **Do not** dispose of your sharps disposal container in household trash unless your community guidelines permit this.
- **Do not** recycle your used sharps disposal container.
- Keep the sharps disposal container out of the reach of children.

10. Expect increased need to urinate

Urine production should increase about an hour after the injection for up to 6 hours. If you do not notice the need to use the bathroom, contact your healthcare provider.

For additional resources call 1-877-323-8505

Patent: www.mannkindcorp.com/patent-notices

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: ##/202#

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