rivfloza®
(nedosiran) injection
80mg, 128mg, 160mg

Prescribing Information

FOR

RIVFLOZA®
(nedosiran) injection

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(nedosiran) injection
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RIVFLOZA® safely and effectively.

Please click here for RIVFLOZA® Prescribing Information.

RIVFLOZA® (nedosiran) injection, for subcutaneous use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

RIVFLOZA® is an *LDHA*-directed small interfering RNA indicated to lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., eGFR ≥30 mL/min/1.73 m^2. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is shown below and is administered subcutaneously once monthly. (2.1)

Age	Body Weight	Dosing Regimen
Adults and adolescents 12 years and older	Greater than or equal to 50 kg	160 mg once monthly (Pre-filled Syringe, 1 mL)
	Less than 50 kg	128 mg once monthly (Pre-filled Syringe, 0.8 mL)
Children 9 to 11 years	Greater than or equal to 50 kg	160 mg once monthly (Pre-filled Syringe, 1 mL)
	Less than 50 kg	3.3 mg/kg once monthly, not to exceed 128 mg (Vial, dose volume rounded to nearest 0.1 mL)

See full Prescribing Information for important administration instructions. (2.2)

DOSAGE FORMS AND STRENGTHS

RIVFLOZA® Injection 160 mg/mL is a clear, colorless-to-yellow solution available as follows:

- 80 mg (0.5 mL) Single-dose Vial
- 128 mg (0.8 mL) Single-dose Pre-filled Syringe
- 160 mg (1 mL) Single-dose Pre-filled Syringe (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

Most common adverse reaction (reported in ≥20% of patients) is injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-844-906-5099 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RIVFLOZA® is indicated to lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., eGFR ≥30 mL/min/1.73 m^2 *[see Clinical Pharmacology (12.3), Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

RIVFLOZA® is administered subcutaneously once monthly at the recommended doses shown in Table 1.

Dosing is based on actual body weight.

Table 1: RIVFLOZA® Dose Regimen in Adults and Pediatric Patients (9 years of age and older)

Age	Body Weight	Dosing Regimen
Adults and adolescents 12 years and older	Greater than or equal to 50 kg	160 mg once monthly (Pre-filled Syringe, 1 mL)
	Less than 50 kg	128 mg once monthly (Pre-filled Syringe, 0.8 mL)
Children 9 to 11 years	Greater than or equal to 50 kg	160 mg once monthly (Pre-filled Syringe, 1 mL)
	Less than 50 kg	3.3 mg/kg once monthly, not to exceed 128 mg (Vial, dose volume rounded to nearest 0.1 mL)

Missed Dose

If a planned dose is missed, administer RIVFLOZA® as soon as possible. If the planned dose is missed by more than 7 days, administer RIVFLOZA® as soon as possible and resume monthly dosing from the most recently administered dose.

2.2 Administration Instructions

Pre-filled syringe: A healthcare professional, caregiver, or patient 12 years of age and older may inject RIVFLOZA® using the pre-filled syringe. In pediatric patients 9 to 11 years of age who weigh ≥50 kg, a healthcare professional or caregiver may inject RIVFLOZA® using the pre-filled syringe.

Vials: RIVFLOZA® Vials are intended for use under the guidance and supervision of a healthcare professional. A caregiver may administer RIVFLOZA® to pediatric patients after proper training in preparing RIVFLOZA® Vials for administration, if a healthcare professional determines that it is appropriate, and with medical follow-up as necessary.

Administer RIVFLOZA® by subcutaneous injection to the abdomen (at least 2 inches from the navel) or the upper thigh. Do not inject into a vein or into scarred or bruised skin.

Inspect visually for particulate matter and discoloration prior to injection. RIVFLOZA® should be colorless-to-yellow and particle free. If the solution is cloudy or contains particulate matter, do not use.

Instructions for delivering the dosage are provided in the Instructions for Use leaflets enclosed with the RIVFLOZA® Pre-filled Syringe and Single-dose Vial.

Discard the unused portion of the drug.

3 DOSAGE FORMS AND STRENGTHS

RIVFLOZA® Injection 160 mg/mL (present as 170 mg nedosiran sodium salt) is a clear, colorless-to-yellow solution available as follows:

- 80 mg (0.5 mL) Single-dose Vial
- 128 mg (0.8 mL) Single-dose Pre-filled Syringe
- 160 mg (1 mL) Single-dose Pre-filled Syringe

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RIVFLOZA® has been evaluated in one placebo-controlled clinical trial (PHYOX2) and one open-label extension study (PHYOX3). Across these studies, 29 adults and 12 children with PH1 have been treated with RIVFLOZA®. Patients with PH1 in these studies ranged in age from 9 to 46 years at first dose. The median duration of exposure was approximately 15 months (range 1 to 29 months). Overall, 38 patients with PH1 were treated for at least 6 months, 24 patients for at least 12 months, and 16 patients for at least 18 months.

In the randomized, placebo-controlled, double-blind PHYOX2 trial in pediatric and adult patients 9 to 46 years of age, 18 patients with PH1 received RIVFLOZA® and 11 patients received placebo. Of the 18 patients treated with RIVFLOZA®, 17 patients received ≥5 months of active treatment. The most common adverse reaction was injection site reactions, which were reported in 7 patients with PH1 (39%) on RIVFLOZA® as compared to no patients on placebo. Injection site reactions included erythema, pain, bruising, and rash and were generally mild and did not lead to discontinuation of treatment.

In the single-arm extension study (PHYOX3) that included 40 patients with PH1, additional injection site reactions included atrophy in 1 patient (3%).

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from reports of pregnancy in clinical trials with RIVFLOZA® are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies, no adverse developmental effects were observed when nedosiran was administered to pregnant mice at doses up to approximately 58 times the maximum recommended human dose (MRHD) of 160 mg nedosiran (equivalent to 170 mg nedosiran sodium) per dose, based on body surface area (BSA) or upon administration of a mouse-specific (pharmacologically active) analog. Subcutaneous administration of nedosiran to pregnant rabbits during the period of organogenesis at doses approximating the MRHD resulted in increased fetal loss in the presence of maternal toxicity. Adverse developmental outcomes (fetal cardiovascular and skeletal malformations) were observed at a dose approximately 2 times the MRHD *(see Data)*. Nedosiran is not pharmacologically active in rabbits or mice. The cause for the embryo-fetal toxicities observed in rabbits remains unclear.

The estimated background risk of major birth defects and miscarriage in the indicated population 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 clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In mice, subcutaneous administration of nedosiran at doses up to 2000 mg/kg/dose (approximately 58 times the MRHD based on BSA) or a mouse-specific (pharmacologically active) analog (10 mg/kg/dose) during organogenesis (dosing on gestation days 6, 8, 10, 12, and 14 for nedosiran; gestation days 3 and 10 for the analog) did not have adverse effects on embryo-fetal development.

Subcutaneous administration of nedosiran (0, 2, 6, or 20 mg/kg/dose) to pregnant rabbits during organogenesis (dosing on gestation days 7, 9, 11, 13, 15, 17, and 19) resulted in maternal toxicity on the basis of body weight loss of up to 6.5% following the first dose in the 6 and 20 mg/kg/dose groups. Higher post-implantation loss and lower numbers of live fetuses occurred at ≥6 mg/kg/dose (exposures equivalent to the MRHD based on BSA), and fetal cardiovascular and skeletal malformations occurred at the 20 mg/kg/dose (2 times the MRHD based on BSA). At the 2 mg/kg/dose, which is below the MRHD, no adverse findings were seen.

In a pre- and postnatal study in mice, subcutaneous administration of nedosiran (0, 250, 500, or 1000 mg/kg/dose) or a mouse-specific (pharmacologically active) analog (10 mg/kg/dose) from implantation (dosing on gestational days 6, 8, 10, 12, 14, 16) to weaning (dosing on lactation days 1, 8, 15, 20) did not have adverse effects on the growth, viability, development and reproductive performance of the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of RIVFLOZA® in human or animal milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RIVFLOZA® and any potential adverse effects on the breastfed infant from RIVFLOZA® or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of RIVFLOZA® have been established in pediatric patients aged 9 years and older. Use of RIVFLOZA® in these age groups is supported by evidence from an adequate and well-controlled trial in adult and pediatric patients 9 years of age and older *[see Clinical Studies (14)]*.

The safety and effectiveness of RIVFLOZA® in patients younger than 9 years of age have not been established.

8.5 Geriatric Use

Clinical studies of RIVFLOZA® did not include patients aged 65 and over to determine whether they respond differently from younger patients. No dose adjustment is recommended in patients ≥65 years old *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dose adjustment of RIVFLOZA® is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin >1 to 1.5 times ULN and any AST).

RIVFLOZA® has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 ULN with any AST) *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is recommended in patients with an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2 *[see Clinical Pharmacology (12.3)]*.

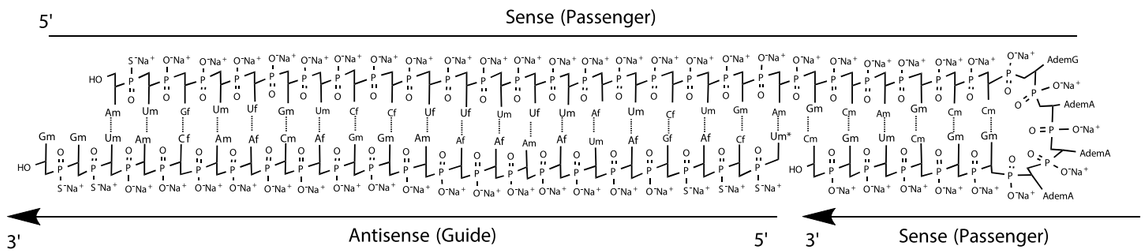
RIVFLOZA® has not been studied in PH1 patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2).

Please click here for RIVFLOZA® Prescribing Information.

11 DESCRIPTION

RIVFLOZA® injection contains nedosiran, a double-stranded small interfering RNA (siRNA) with four covalently attached *N*-acetyl-D-galactosamine (GalNAc) residues. Nedosiran targets lactate dehydrogenase A (LDHA) in hepatocytes via GalNAc-mediated delivery.

The structural formula of the nedosiran sodium drug substance is presented below:



The molecular formula of nedosiran sodium is $C_{662}H_{808}F_{19}N_{231}O_{413}P_{57}S_6Na_{57}$ with a molecular weight of 22,238 Da. Nedosiran sodium is freely soluble in water.

RIVFLOZA® Pre-filled Syringe is supplied as a clear, sterile, preservative-free, colorless-to-yellow solution for subcutaneous injection containing either the equivalent of 160 mg (present as 170 mg nedosiran sodium salt) nedosiran in 1 mL or the equivalent of 128 mg (present as 136 mg nedosiran sodium salt) nedosiran in 0.8 mL of water for injection and sodium hydroxide and/or hydrochloric acid to adjust the pH to ~7.2.

RIVFLOZA® Vial is supplied as a clear, sterile, preservative-free, colorless-to-yellow solution for subcutaneous injection containing the equivalent of 80 mg (present as 85 mg nedosiran sodium salt) nedosiran in 0.5 mL of water for injection and sodium hydroxide and/or hydrochloric acid to adjust the pH to ~7.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nedosiran is a double-stranded siRNA, conjugated to GalNAc aminosugar residues. After subcutaneous administration, the GalNAc-conjugated sugars bind to asialoglycoprotein receptors (ASGPR) to deliver nedosiran to hepatocytes.

Nedosiran reduces levels of hepatic lactate dehydrogenase (LDH) via the degradation of LDHA messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. The reduction of hepatic LDH by nedosiran reduces the production of oxalate by the liver, thereby reducing subsequent oxalate burden.

12.2 Pharmacodynamics

The pharmacodynamic effects of RIVFLOZA® were evaluated after Single-dose and monthly-dose administration in patients with PH1. Dose-dependent reductions in urinary oxalate were observed in the single-dose range of 1.5 mg/kg to 6.0 mg/kg. With the recommended monthly dose regimen of RIVFLOZA®, onset of effect was observed at the first measurement (30 days after the first dose) and the effect persisted with continued monthly dosing *[see Clinical Studies (14.1)]*.

Cardiac Electrophysiology

At the recommended dose, RIVFLOZA® does not lead to clinically relevant QT interval prolongation.

12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of RIVFLOZA® were evaluated following administration of single and multiple dosages in patients with PH1 or PH2 as summarized in Table 2.

Table 2: Pharmacokinetic Parameters of Nedosiran

		Nedosiran
General Information		
Steady State Exposure	C_{max} [Mean (%CV)]	844 (44) ng/mL
	$AUC_{0\text{-last}}$ [Mean (%CV)]	13600 (36) ng*h/mL
Dose Proportionality		Nedosiran exhibited a dose-proportional increase in plasma exposure following single subcutaneous doses from 1.5 to 6.0 mg/kg. Nedosiran exhibited time-independent pharmacokinetics with multiple doses of 160 mg once monthly (body weight ≥50 kg), 128 mg once monthly (body weight <50 kg), or 3.3 mg/kg once monthly in the age range of 6 to 11 years.
Accumulation		No accumulation of nedosiran was observed in plasma following repeated monthly dosing.

Please click here for RIVFLOZA® Prescribing Information.

Table 2: Pharmacokinetic Parameters of Nedosiran, continued

	Nedosiran
General Information	
Absorption	
T_{max} [Median (Range)]	6 (2 to 12) hours
Distribution[a]	
Estimated Vz/F	126 L
Protein Binding	85.6%
Elimination	
Half-Life [Mean (%CV)]	15 (68) hours
Estimated CL/F	5.7 L/hr
Metabolism	
Primary Pathway	Nedosiran is metabolized by endo- and exonucleases to shorter oligonucleotides.
Excretion	
Primary Pathway	Approximately 27% of the administered nedosiran dose is excreted unchanged into the urine within 24 hours of dosing.

[a] Nedosiran distributes primarily to the liver after subcutaneous administration.

C_{max} = maximum plasma concentration; $AUC_{0\text{-}last}$ = area under the plasma concentration-time curve from time of administration (0) to the last measurable time point (last); T_{max} = time to maximum concentration; Vz/F = apparent volume of distribution; CV = coefficient of variation; CL/F = apparent clearance.

Specific Populations

No clinically significant differences in the pharmacokinetics or pharmacodynamics of nedosiran were observed based on age (9 to 73 years old), sex, race/ethnicity, mild-to-moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2) *[see Use in Specific Populations (8.7)]* or mild hepatic impairment as assessed using the National Cancer Institute Organ Dysfunction Working Group criteria (total bilirubin ≤ULN and AST >ULN; or total bilirubin >1 to 1.5 × ULN and any AST) *[see Use in Specific Populations (8.6)]*.

Pediatrics:

At the recommended clinical dose, PK exposure of nedosiran is similar in adult and pediatric patients 9 years of age and older.

Drug Interaction Studies

Concomitant use of pyridoxine (vitamin B6) did not have a significant impact on the PK of nedosiran.

In vitro studies demonstrated that nedosiran was not an inhibitor or inducer of cytochrome P450 (CYP) enzymes and was neither a substrate nor an inhibitor of efflux and uptake transporters.

12.6 Immunogenicity

As with all oligonucleotides, including RIVFLOZA®, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Across all clinical studies in the nedosiran development program, including patients with PH1 dosed with RIVFLOZA®, RIVFLOZA® did not induce or boost anti-drug antibodies (ADA). Among 59 patients tested with the ADA assay, none developed treatment-emergent ADA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Long-term studies to assess carcinogenic risk of nedosiran have not been conducted.

Genotoxicity

Nedosiran was not genotoxic in the in vitro bacterial mutagenicity, in vitro micronucleus assays (human peripheral blood lymphocytes) and in vivo bone marrow micronucleus assay in mice.

Fertility

Weekly subcutaneous administration of nedosiran at doses of 500, 1000, or 2000 mg/kg or of a mouse-specific (pharmacologically active) analog at a dose of 10 mg/kg to male mice for 4 weeks prior to and throughout mating, and to female mice for 2 weeks prior to and throughout mating and to gestation day 7 did not affect male or female fertility or early embryonic development.

Please click here for RIVFLOZA® Prescribing Information.

14 CLINICAL STUDIES

14.1 PHYOX2

PHYOX2 was a randomized, double-blind trial comparing RIVFLOZA® and placebo in patients aged 6 years or older with PH1 or PH2 and an eGFR ≥30 mL/min/1.73 m^2 (NCT03847909). Too few PH2 patients were enrolled to evaluate efficacy in the PH2 population. Therefore, RIVFLOZA® is only indicated for patients with PH1 *[see Indications and Usage (1)]*. Unless otherwise noted, data are presented for the complete study population (PH1 and PH2).

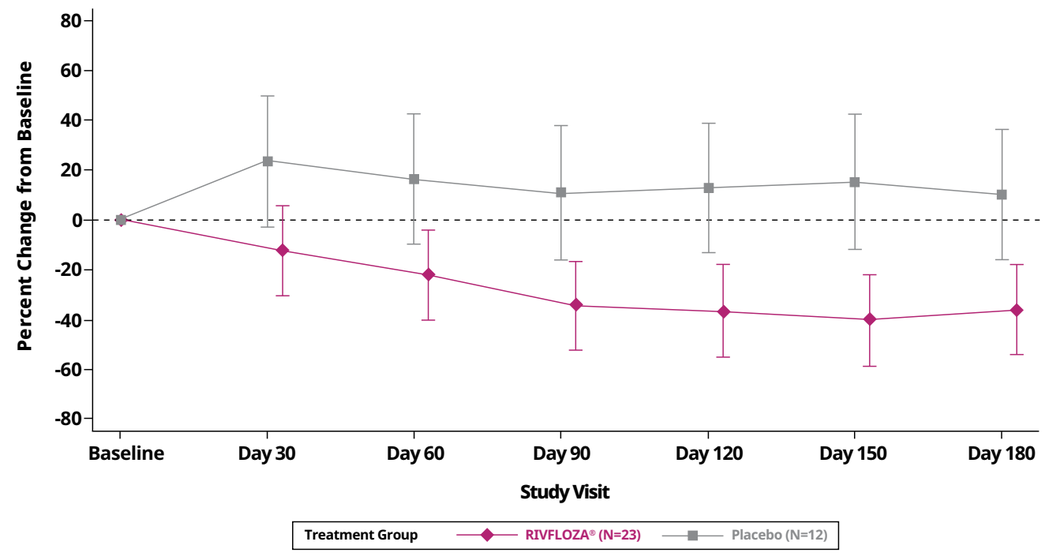
Patients received monthly doses of RIVFLOZA® (N=23) or placebo (N=12). The RIVFLOZA® dose for patients at least 12 years of age weighing at least 50 kg was 160 mg, for patients at least 12 years of age weighing less than 50 kg was 128 mg, and for children 6 to 11 years of age was 3.3 mg/kg (to a maximum of 128 mg).

The median age was 20 years (range 9 - 46 years), 51% were female, 71% were White, 17% were Asian, 83% had PH1, and 17% had PH2. At baseline, mean 24-hour urinary oxalate excretion, normalized by 1.73 m^2 BSA in patients less than 18 years of age, was 1547 µmol/24-hour. Mean plasma oxalate was 8.2 µmol/L, 43% of patients had an eGFR ≥90 mL/min/1.73 m^2, 34% had an eGFR 60 to <90 mL/min/1.73 m^2, 23% had an eGFR 30 to <60 mL/min/1.73 m^2, and 60% were taking pyridoxine.

The primary efficacy endpoint was the area under the curve, from Days 90 to 180, of the percent change from baseline in 24-hour urinary oxalate excretion ($AUC_{24\text{-hour Uox}}$). The least-squares (LS) mean $AUC_{24\text{-hour Uox}}$ was -3486 (95% CI: -5025, -1947) in the RIVFLOZA® group compared to 1490 (95% CI: 781, 3761) in the placebo group, for a between group difference of 4976 (95% CI: 2803, 7149; p<0.0001).

The LS mean percent change from baseline in 24-hour urinary oxalate excretion (corrected for BSA in patients <18 years of age) averaged over Days 90, 120, 150, and 180, was -37% (95% CI: -53%, -21%) in the RIVFLOZA® group and 12% (95% CI: -12%, 36%) in the placebo group, for a between group difference of 49% (95% CI: 26%, 72%) [Figure 1]. Among patients with PH1, the between group difference was 56% (95% CI: 33%, 80%).

Figure 1. Mean (95% CI) Percent Change from Baseline in 24-hour Urinary Oxalate in RIVFLOZA® and Placebo-Treated Patients in PHYOX2



After 6 months of treatment in PHYOX2, patients could enroll in an ongoing single-arm extension study, PHYOX3 (NCT04042402), in which all patients were treated with RIVFLOZA®. The reduction in urinary oxalate was maintained in the 13 patients with PH1 who received an additional 6 months of treatment in PHYOX3.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RIVFLOZA® is a clear, sterile, preservative-free, colorless-to-yellow solution available in single-dose pre-filled syringes and single-dose vials in cartons containing one unit each.

Table 3: RIVFLOZA® Presentations

RIVFLOZA® Presentation	Total Volume	Total amount available in presentation	Concentration	NDC number
Single-dose Vial	0.5 mL	80 mg	160 mg / mL	NDC 0169-5308-01
Single-dose Pre-filled Syringe	0.8 mL	128 mg	160 mg / mL	NDC 0169-5307-08
Single-dose Pre-filled Syringe	1 mL	160 mg	160 mg / mL	NDC 0169-5306-10

16.2 Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F). RIVFLOZA® can be stored, if needed, at 15°C to 30°C (59°F to 86°F) for a maximum of 28 days (4 weeks). Do not freeze. Store in original carton, away from direct heat and light.

Table 4: Storage Conditions for RIVFLOZA®

	Refrigerated 2°C to 8°C (36°F to 46°F)	Room Temperature at 15°C to 30°C (59°F to 86°F)
RIVFLOZA®	Until expiration date	Maximum 28 days (4 weeks)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

- Instruct patients/caregivers on the appropriate dose of RIVFLOZA® to use, the timing of the dose, how and where to inject subcutaneously, and what to do if a dose is missed.

For more information contact:
Dicerna Pharmaceuticals, Inc.
A Novo Nordisk company

Novo Nordisk Inc
800 Scudders Mill Road
Plainsboro, NJ 08536
1-844-906-5099

Manufactured by
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3598 Cadillac Ave
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