CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215842Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215842
PDUFA Goal Date	September 30, 2023
Nexus TTT #	2022-2726
Reviewer Name	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Director	Laura Zendel, PharmD
Review Completion Date	September 28, 2023
Subject	Evaluation of Need for a REMS
Established Name	nedosiran
Trade Name	Rivfloza
Name of Applicant	Novo Nordisk Inc
Therapeutic Class	Small interfering RNA
Formulation(s)	Injection (160 mg/mL) 160 mg (1 mL) single-dose pre-filled syringe (PFS) 128 mg (0.8 mL) single-dose PFS 80 mg (0.5 mL) single-dose vial
Dosing Regimen	Once a month subcutaneous injection, fixed dose based on weight for patients 12 years of age and older, weight-based for patients (b) (4) to less than 12 years of age.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rivfloza (nedosiran) is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc submitted a New Drug Application (NDA) 215842 for nedosiran with the proposed indication for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric ((b) (4) years of age and older) and adult patients. No serious risks are associated with nedosiran. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of nedosiran outweigh its risks. The review team concluded the data presented provide compelling evidence of benefit to patients with the rare, serious disease of PH1. If approved, the indication for nedosiran will be 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/m^2. Nedosiran was well-tolerated and the majority of adverse events associated with nedosiran are of mild to moderate severity. At the time of this review, the review team determined that a boxed warning and warnings and precautions are not necessary to include in labeling, however, labeling will describe the most common adverse events.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rivfloza (nedosiran) is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. submitted a New Drug Application (NDA) 215842 for nedosiran with the proposed indication for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric ((b) (4) years of age and older) and adult patients. This application is under review in the Division of Cardiology and Nephrology (DCN). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Rivfloza (nedosiran), a new molecular entity[a], is a small interfering RNA (siRNA) proposed for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric ((b) (4) years of age and older) and adult patients. Nedosiran is a synthetic, double-stranded siRNA conjugated to an N-acetyl-D-galactosamine (GalNac) ligand. The ligand is designed to target delivery to hepatocytes via asialoglycoprotein receptors (ASGR). Nedosiran inhibits messenger RNA of the lactate dehydrogenase A (LDHA) gene, which encodes LDH, the enzyme that metabolizes glyoxylate to oxalate. Suppression of LDH should, therefore, reduce hepatic oxalate production, in turn reducing oxaluria and its sequelae.[1] Nedosiran was granted breakthrough therapy and orphan drug designation and is not currently approved in any jurisdiction.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Nedosiran is proposed as a once monthly subcutaneous injection to be used chronically and may continue indefinitely[b]. Nedosiran is proposed to be available as a 160 mg/1 ml single-dose prefilled syringe (PFS), 128 mg/0.8 ml single-dose PFS, and 80 mg/0.5 ml single-dose vial. The Applicant proposes nedosiran as a self-injection or to be given by a patient's caregiver.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215842 relevant to this review:

- 5/15/2018: Orphan Drug designation granted
- 7/2/2019: Breakthrough Therapy designation granted
- 3/25/2020: Rare Pediatric Disease designation granted
- 9/30/2022: Applicant submitted the final submission to complete the rolling submission for NDA 215842 for the treatment of primary hyperoxaluria Type 1
- 3/13/2023: Applicant informed at Mid-cycle teleconference that no major safety concerns have been identified at this time
- 6/5/2023: Applicant informed at Late-cycle teleconference of major labeling issues

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

PH1 is a rare, serious, genetic disease that often manifests in childhood or adolescence. PH1 is caused by an inherited deficiency of the liver enzyme alanine-glyoxylate aminotransferase (AGT) that leads to overproduction of oxalate by the liver. To date, three types of PH have been described, defined by the affected gene. PH1 accounts for 70-80% of primary hyperoxaluria cases and is the most clinically severe. Patients with PH1 have recurrent kidney stones and can have deposition of calcium in the kidneys leading to a loss of kidney function. As kidney function declines, oxalate accumulates in the body and deposits in other tissues. Systemic manifestations include arrhythmias, cardiac arrest, gangrene, bone/joint pain and fractures, blindness, subcutaneous nodules, plaques or ulceration, pancytopenia, and hypothyroidism.[c] When moderate to severe kidney failure develops, patients often require a period of intensive dialysis and a combined or sequential liver and kidney transplant. PH1 is a devastating, progressive, and debilitating disease. PH1 is an orphan disease. The global prevalence of Primary

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Hyperoxalurias ranges from 1 – 3 per 1,000,000.[2] The Applicant estimates a US prevalence of PH1 to be 2,692 people[d] based on a 2018 total US population estimate of 327 million people.[3]

3.2. Description of Current Treatment Options

Oxlumo (lumasiran) is a siRNA which reduces levels of the glycolate oxidase (GO) enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes. Lumasiran was approved in 2020 to lower urinary and plasma oxalate levels in pediatric and adults patients with PH1 with relatively preserved kidney function based on treatment effects of high baseline urinary oxalate (Uox) levels. Pyridoxine, a coenzyme of AGT, may reduce hepatic oxalate production in patients with certain genetic mutations. Standard of care therapies for primary hyperoxaluria include high fluid intake and medications like citrate and magnesium to reduce calcium oxalate crystallization; however, many patients progress despite these interventions. Liver transplant replaces the missing AGT enzyme and is essentially curative but is associated with substantial morbidity. There is an unmet need for additional therapies to treat PH1.[1]

Three other siRNA-based therapies are approved for managing rare metabolic disease such as hereditary transthyretin amyloidosis (hATTR), acute hepatic porphyria (AHP), and heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD). None of the four FDA-approved siRNA-based therapies has a REMS or *Boxed Warning*.[4]

4. Benefit Assessment

The efficacy and safety of nedosiran for PH1 was demonstrated in a phase 2 study [DCR-PHXC-201; PHYOX2; NCT 03847909] and a phase 3 extension study [DCR-PHXC-301; PHYOX3; NCT 04042402]. The Applicant designed phase 2 Study DCR-PHXC-201 to support an indication for PH1 and PH2. DCR-PHXC-201 was a six-month double-blind, randomized, placebo-controlled, multicenter trial in which 35 patients aged 6 years or older were randomized 2:1 to nedosiran or placebo for 6 months. Eligible participants who completed the study could receive nedosiran in a long-term open-label extension study, DCR-PHXC-301. The primary endpoint for DCR-PHXC-201 was the area under the curve (AUC) of percent change in 24-hour urinary oxalate excretion from baseline over the last 3 months of treatment. Urinary oxalate is a surrogate for kidney stones and loss of kidney function in patients with PH1 with relatively preserved kidney function (eGFR >30 mL/min/1.73 m^2 or serum creatinine within normal for patients <12 months of age) and plasma oxalate is a surrogate for the systemic manifestations of PH1 in patients with an eGFR <30 mL/min/1.73 m^2 including patients on hemodialysis.[1]

After evaluation of the results of DCR-PHXC-201, the Applicant informed the Agency that approval would be sought for PH1 only due to lack of PH2 patients in the control arm of the study. The Agency then requested that the Applicant provide all pre-specified primary endpoint and additional analyses to assess the impact of imbalances on the efficacy findings.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

In Study DCR-PHXC-201 twenty-eight patients had PH1; 17 randomized to nedosiran and 11 to placebo. The study met its primary endpoint for the population as a whole (PH1 and PH2, the initial trial design) as well as PH1 only (post-hoc trial design). The least-squares (LS) mean AUC of percent change in 24-hour Uox from baseline was 3486 (95% CI 1947, 5025) in the nedosiran group and -1490 (95% CI -3761, -781) in the placebo group, for a between-group difference of 4976 (95% CI 2803, 7149; p<0.0001). The primary endpoint does not describe the magnitude of change in Uox from baseline to Month 6 in a way that is readily understandable; hence, the review team also evaluated the LS mean percent change in 24-hour Uox excretion (corrected for BSA in patients <18 years of age) from baseline to Day 180 (mean of Days 90 to 180).[1] The LS mean percent change from baseline was -37% (95% CI -53%, -21%) in the nedosiran group and 12% (95% CI 12%, 36%) in the placebo group, for a between-group difference of -49% (95% CI -26%, -72%).[1] Among patients with PH1, between-group difference was -56% (95% CI -80%, -33%).[1] The reduction in urinary oxalate was maintained in 13 patients with PH1 who received 6 months of treatment with nedosiran in Study DCR-PHXC-201 and an additional 6 months of treatment in Study DCR-PHXC-301.[1] The review team concluded that the submitted data provide evidence that nedosiran reduces Uox, a surrogate for important clinical manifestations of PH1, and provides compelling evidence for approval.[1e]

5. Risk Assessment & Safe-Use Conditions

Potential adverse events or toxicities associated with GalNAc-conjugated siRNA products include injection site reactions, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations, mild increases in serum creatinine and decreases in estimated glomerular filtration rate (eGFR), positive adenosine deaminase (ADA), and hypersensitivity (including anaphylactic reactions). Due to the mechanism of action of nedosiran, elevations of glycolate in plasma and urine are expected in patients with PH1. Effects of chronic elevations of glycolate are unknown, but the review team concluded that the available data suggest these elevations are benign.[1]

The safety database for nedosiran, consisting of studies DCR-PHXC-201 and DCR-PHXC-301 analyzed individually, is limited as expected given the estimated incidence in the US of the rare disease PH1. In Study DCR-PHXC-201, most treatment emergent adverse events (TEAEs) were mild or moderate in severity consisting of local administration reactions followed by hemorrhage, nausea, and bacterial infection. One patient (4%) in the nedosiran arm and two (17%) in the placebo arm experienced a serious adverse event (SAE). The patient who experienced a SAE (tachycardia) in the nedosiran arm discontinued treatment and withdrew consent because of the SAE. One patient in the placebo group with PH1 discontinued study drug because of an SAE of blood creatinine increased, progression of CKD and initiation of dialysis. One patient in the placebo group experienced nephrolithiasis and renal colic. There were no deaths.[1]

In Study DCR-PHXC-301, 47 patients (92%) experienced a TEAE and most were mild. Four patients (8%) experienced SAEs and three patients (6%) interrupted dosing because of an AE. The clinical reviewer concluded the SAEs of pyelonephritis, acute kidney injury, calculus urinary, and nephrolithiasis are consistent with comorbidities seen in the study population.[1] The SAEs of abdominal pain and pain in the

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

extremity were likely not caused by nedosiran.[1] In Study DCR-PHXC-301, no patients discontinued nedosiran because of AEs and there were no deaths.

Nedosiran was well-tolerated. The most common adverse events were injection site reactions (reported in ≥20% of patients), which were generally mild, and did not lead to treatment discontinuation. Nausea occurred more frequently in patients treated with nedosiran compared with placebo. There was no evidence of hepatic toxicity or myopathy/rhabdomyolysis based on either adverse events or laboratory tests; however, the clinical reviewer acknowledged the safety database is limited.[1] At the time of this review, the label for nedosiran does not contain a Boxed Warning or Warnings and Precautions, and has no Contraindications however, labeling will describe the most common adverse events including injection site reactions.

6. Expected Postmarket Use

Nedosiran is expected to be prescribed by physicians who are experienced in PH1 treatment. Pediatric and adult patients with PH1 are followed by hepatologists, nephrologists and other specialists who monitor disease progression and complications in the outpatient and inpatient settings.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for nedosiran beyond routine pharmacovigilance and labeling.

Novo Nordisk Inc[5] states that:

> Taken together, the Sponsor believes the Benefit-Risk ratio of nedosiran to be positive, the findings from the PHYOX2 and PHYOX3 studies support that nedosiran was highly effective in reducing the hepatic production of oxalate in patients with PH1, as measured by multiple indices of oxalate burden, including urinary oxalate and plasma oxalate, as well as positive trends in the clinical endpoints of stone burden and stone event rate. Additionally, a greater percentage of patients in the placebo arm than the nedosiran experienced one or more kidney stone events in the 6-month PHYOX2 study (42% vs. 13 %, respectively). [...]
>
> With all the evidence provided the Sponsor believes that a Risk Evaluation & Mitigation Strategy (REMS) is not required for nedosiran, beyond routine pharmacovigilance and labeling activities.

8. Discussion of Need for a REMS

The review team believes the data provide compelling evidence of a benefit that outweighs the risks and recommends approval.[1] Given that the study did not enroll patients less than 9 years of age, the indication will be limited to patients ≥9 years of age with PH1. The FDA approved indication for nedosiran will be 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/m^2.

Nedosiran was well-tolerated and there were no apparent significant or irreversible toxicities observed in the trials.

Nedosiran has a comparable safety profile to lumasiran, another siRNA approved for a similar indication. No significant safety issues were identified in the clinical development program for either product, and no additional risk minimization measures are considered necessary. Labeling is sufficient to communicate the adverse events expected with nedosiran treatment including injection site reactions. Based on the data available and the prescribing community's likely familiarity with managing injection site reactions, a common risk associated with injectable drug products, DRM is not recommending a REMS for nedosiran at this time.

9. Conclusion & Recommendations

Based on the integrated review, the data provide compelling evidence of a benefit that outweighs the risks, therefore, a REMS is not necessary for nedosiran to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Division of Cardiology and Nephrology (DCN), DRAFT Integrated Review for Rivfloza (nedosiran) NDA 215842, September 1, 2023.

[2] Groothoff, J.W. and Hoppe, B. Orpha.net Primary Hyperoxaluria disease summary, January 2020. Available from https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=416

[3] Dicerna Pharmaceuticals, Inc. Orphan Drug Designation Application for DCR-PHXC (nedosiran), March 19, 2018 included in September 30, 2022 submission for nedosiran (NDA 215842) by Novo Nordisk Inc.

[4] Padda I.S. et al. Small Interfering RNA (siRNA) Therapy. In StatPearls [Internet], Updated June 3, 2023. Available from https://www.ncbi.nlm.nih.gov/books/NBK580472/

[5] Novo Nordisk Inc. Risk Management (Non-REMS) for Rivfloza (nedosiran) NDA 215842, September 30, 2022.

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