

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212154Orig1s000

**RISK ASSESSMENT AND RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
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	212154
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Reviewer Names	Jacqueline Sheppard, PharmD Lindsey Crist, PharmD, BCPS
Team Leader	Laura Zendel, PharmD
Acting Division Director	Doris Auth, PharmD
Review Completion Date	August 4, 2020
Subject	Evaluation of Need for a REMS
Established Name	Viltolarsen
Trade Name	Viltepso
Name of Applicant	Nippon Shinyaku Co, Ltd.
Therapeutic Class	Antisense oligonucleotide
Formulation	Solution for injection
Dosing Regimen	80 mg/kg administered by intravenous infusion once weekly

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Viltespo (viltolarsen) is necessary to ensure the benefits outweigh its risks. Nippon Shinyaku Co, Ltd. (NS Pharma) submitted a New Drug Application (NDA 212154) for viltolarsen with the proposed indication for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. The risks associated with viltolarsen include potential renal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and the Division of Neurology 1 (DN1) agree that a REMS is not needed to ensure the benefits of viltolarsen outweigh its risks. Viltolarsen meets the accelerated approval criteria by having the potential to address an unmet need in a serious and life-threatening disease, by having an advantage over available therapies, and the prior approval of other antisense oligonucleotides that increase amounts of truncated dystrophin to achieve likely clinical benefit. The side effect profile of viltolarsen is similar to other antisense oligonucleotides (including potential risk of renal toxicity with golodirsen) and prescribers are likely to be familiar with and able to appropriately monitor for this risk. Additionally, the risk of potential renal toxicity will be included in the Warning and Precautions section of the label where prescribers will be instructed to monitor renal function.

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) Viltespo (viltolarsen) is necessary to ensure the benefits outweigh its risks. Nippon Shinyaku Co, Ltd. (NS Pharma) submitted a New Drug Application (NDA 212154) for viltolarsen with the proposed indication for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This application is under review in the Division of Neurology 1 (DN1). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Viltolarsen, a new molecular entity (NME)^a, is an antisense oligonucleotide proposed for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Viltolarsen binds to exon 53 of the dystrophin pre-mRNA transcript resulting in exclusion of this exon (exon skipping) during mRNA processing resulting in production of an internally shortened, but potentially functional dystrophin protein. It is theorized that increases in dystrophin levels in patients with DMD may result in clinical benefit.

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

Viltolarsen is proposed to be supplied as a 250 mg/5 mL (50 mg/mL) solution administered as 80 mg/kg intravenous infusion once weekly for the lifetime of the patient.^b Viltolarsen was granted fast track designation on October 25, 2016, orphan drug designation on January 12, 2017, and Rare Pediatric Disease designation on January 24, 2017. Viltolarsen is not approved in any jurisdiction at this time.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for viltolarsen, NDA 212154, relevant to this review:

- 10/25/2016: Fast Track designation granted for the treatment of DMD.
- 01/12/2017: Orphan drug designation granted for the treatment of DMD.
- 01/24/2017: Rare Pediatric disease designation granted for the treatment of DMD.
- 01/19/2019: Rolling review request granted.
- 11/4/2019: Filing meeting held and determined the application was incomplete due to missing information regarding validation of assays. The Agency issued an information request to the Applicant for the additional validation data.
- 12/12/2019: The final portion of a rolling original NDA received for viltolarsen (NDA 212154).
- 12/12/2019: Priority review granted.
- 03/25/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for viltolarsen.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

DMD is a rare, incurable X-linked recessive, neuromuscular disorder affecting approximately 1 in every 3500 to 5000 male births worldwide.^{1,2,c} The prevalence of DMD in the United States is estimated around 16 cases per 100,000 live male births.³ DMD is caused by mutations in the gene encoding dystrophin, a protein critical to the structural stability of myofibers in skeletal and cardiac muscle. The majority of mutations are deletions that cause a disruption in the mRNA reading frame and prevent the production of functional dystrophin. The absence of dystrophin causes degeneration of muscle fibers, inflammation, and replacement of muscle by fibrotic and adipose tissue. The clinical course is characterized by progressive muscle weakness that is typically diagnosed by the age of five years. Muscle degeneration worsens throughout childhood and adolescence resulting in the loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence,

^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 (A): The estimated size of the population likely to use the drug involved.*

cardiomyopathy, and death.^d Patients often die in their late teens to twenties, usually due to cardiac or respiratory failure.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are limited treatment options for DMD. Glucocorticoid therapy is the mainstay of treatment for most patients with DMD and is associated with an increase in strength, muscle function, and pulmonary function, although the duration of benefit is uncertain. Deflazacort (Emflaza), a systemic corticosteroid, was approved in February 2017 for the treatment of DMD in patients 2 years of age and older.⁶ Risks associated with deflazacort include weight gain, Cushingoid appearance, cataracts, gastrointestinal symptoms, behavioral changes, acne, and excessive hair growth.⁷ Non-pharmacologic treatments include supportive therapies including physical therapy and use of assistive devices (e.g. braces or wheelchairs), surgery, and respiratory and cardiac support.

Exon skipping therapy with antisense oligonucleotides is an emerging treatment option for DMD patients with amenable mutations. Eteplirsen (Exondys 51) is an antisense oligonucleotide approved on September 19, 2016 with the indication for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The main risks associated with eteplirsen are hypersensitivity reactions including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension. A second antisense oligonucleotide, golodirsen (Vyondys 53) was approved on December 12, 2019 for the treatment of DMD in pediatric and adult patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. The risks associated with golodirsen include hypersensitivity reactions and renal toxicity. Both antisense oligonucleotides were approved using the accelerated approval pathway based on the demonstration of a small increase in dystrophin in clinical trials. If approved, viltolarsen would be the second agent available for DMD patients with confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

4 Benefit Assessment

The effect of viltolarsen on dystrophin production was evaluated in a single, 2-period, dose-finding study (NS-065-201 [Study 201], NCT02740972) in biologically male patients between the ages of 4 and <10 with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping who have been on a stable corticosteroid regimen for at least 3 months. The initial four weeks of Study 201 consisted of a multi-center, randomized, double-blind placebo-controlled study where patients were randomized to either Viltepso (n=8) or placebo (n=8). Following the initial phase, all patients then received 20 weeks of open label Viltepso 40 mg/kg/week (n=8) or 80 mg/kg/week (n=8) by intravenous infusion. Efficacy was assessed based on change from baseline in dystrophin protein level at week 25. At week 25, there was a statistically significant increase from baseline in mean dystrophin level with viltepso 80 mg/kg as

^d 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.*

measured by Western Blot (3.8, p=0.01) and nominally statistically significant increases as measured by mass spectroscopy (1.9, p=0.03).

According to the clinical reviewer⁸, the pivotal study effectively demonstrated that viltolarsen increases dystrophin levels. Changes in the surrogate endpoint of dystrophin levels have been determined by the Agency to be reasonably likely to predict clinical benefit based on the approval of eteplirsen and golodirsen, the other antisense oligonucleotide agents approved for DMD. The Clinical Reviewer further states that viltolarsen also meets the other two criteria for accelerated approval: DMD being a serious life-threatening condition and conferring meaningful advantage over other available therapies.

5 Risk Assessment & Safe-Use Conditions

The safety database for viltolarsen is comprised of 32^e genetically male patients with DMD exposed to viltolarsen once weekly in doses ranging from 40mg/kg to 80mg/kg for 20 to 24 weeks. The safety database also includes the 16 patients who were exposed to viltolarsen for durations greater than one year in the ongoing open label extension of Study 201. The most commonly observed adverse events included upper respiratory tract infection (63%), injection site reaction (25%), cough (19%), and pyrexia (19%).

5.1 RENAL TOXICITY

Non-clinical studies of viltolarsen in mice and monkeys showed evidence of renal tubular toxicity but no evidence of glomerular toxicity. Additionally, renal toxicity including elevations in serum creatinine, proteinuria, acute kidney injury, and acute glomerulonephritis have been observed in other antisense oligonucleotides. The Division of Cardiology and Nephrology was consulted for a review of the renal toxicity and safety monitoring of viltolarsen. Per the nephrology reviewer, there was no obvious signal for renal toxicity based on either laboratory data or renal-related adverse events, though it was noted the safety database was limited in size and duration. The nephrology reviewer concludes that based on the preclinical findings and experience with other antisense oligonucleotides “it would be reasonable to include a Warning and Precaution for renal toxicity⁹.” As noted in labeling for other antisense oligonucleotides, the labeling for viltolarsen will recommend that prescribers monitor kidney function. Because of the effect of reduced skeletal muscle mass on serum creatine measurements, serum creatinine may not be a reliable measurement of kidney function in DMD patients. Instead, the labeling will recommend monitoring serum cystatin C and urine protein-to-creatinine ratio prior to and during treatment.

6 Expected Postmarket Use

^e Safety database was comprised of 16 patients from Study 201 and 16 patients from Study NS065/NCNP01 which was a 24-week study not considered supportive of dystrophin expression due to inadequacy to dystrophin assessment methodology. The open label extension study was a continuation of patients in Study 201.

Viltolarsen is likely to be prescribed by neurologists, primary care providers and other members of multidisciplinary clinical teams that manage DMD patients. These prescribers are likely to be familiar with the adverse effects including potential renal toxicity associated with viltolarsen and the other antisense oligonucleotides. Viltolarsen will be used in the inpatient setting or given outpatient in an infusion center or clinic.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for viltolarsen beyond routine pharmacovigilance and labeling. If approved, viltolarsen would be subject to postmarketing requirements including a confirmatory study.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of viltolarsen based on meeting the accelerated approval criteria.

DMD is associated with significant morbidity and mortality with patients often dying in their late teens to twenties due to cardiac or respiratory failure. There are currently three FDA approved treatments for DMD. Viltolarsen offers an additional agent for DMD patients with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

During the clinical development program, use of viltolarsen resulted in a statistically significant increase from baseline in mean dystrophin level. Viltolarsen meets the accelerated approval criteria by having the potential to address an unmet need in a serious and life-threatening disease, by having an advantage over available therapies, and the prior approval of other antisense oligonucleotides that increase amounts of truncated dystrophin to achieve likely clinical benefit.

Clinical data does not show an obvious signal for renal toxicity based on either laboratory data or renal-related adverse events; however, evidence of renal toxicity was found in animals during nonclinical studies and the clinical safety database was small. Prescribers are likely to be familiar with the potential renal toxicity associated with viltolarsen as the risk of adverse events (including potential renal toxicity with golodirsen) is well documented for the other approved antisense oligonucleotides used to treat DMD. Additionally, the risk of potential renal toxicity will be included in the Warning and Precautions section of the label and prescribers will be instructed to monitor renal function.

Overall, the clinical reviewer concludes the safety profile of viltolarsen is acceptable. Based on the data available, the seriousness of the disease state, and the prescribing community's likely familiarity with the risks associated with viltolarsen which do not pose unique REMS considerations compared with the risks associated with other therapies, this reviewer has concluded that a REMS is not necessary to ensure the benefits outweigh the risks of viltolarsen.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The side effect profile is similar to other antisense oligonucleotides including the potential risk of renal toxicity and prescribers are likely to be familiar with and able to appropriately monitor for the risks. At the time of this review, labeling negotiation 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

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