CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217388Orig1s000

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	217388
PDUFA Goal Date	December 22, 2023
OSE TTT#	2022-3161
Reviewer Name(s)	May Chan-Liston, PharmD, MPH
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 19, 2023
Subject	Evaluation of Need for a REMS
Established Name	Eplontersen
Trade Name	Wainua
Name of Applicant	Ionis Pharmaceuticals, Inc
Therapeutic Class	transthyretin-directed antisense oligonucleotide
Formulation(s)	Subcutaneous injection: 45 mg/0.8 mL (56 mg/mL) of eplontersen as a clear, colorless-to-yellow solution in a single-dose autoinjector
Dosing Regimen	Administer Wainua 45 mg once monthly as a subcutaneous injection in the abdomen, upper thigh region, or for caregivers only, the back of the upper arm.

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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 Wainua (eplontersen) is necessary to ensure the benefits outweigh its risks. Ionis Pharmaceuticals, Inc submitted a New Drug Application (NDA 217388) with the proposed indication for the treatment of the polyneuropathy (PN) of hereditary transthyretin-mediated amyloidosis (ATTRv) in adults. The risk associated with eplontersen is vitamin A deficiency which may contribute to ocular changes. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Neurology 1 (DN1) have determined that a REMS is not needed to ensure the benefits of eplontersen outweigh its risks. The safety data generated from clinical trials demonstrate that eplontersen 45 mg given subcutaneously every 4 weeks, has an acceptable safety and tolerability profile compared with external placebo and the historical inotersen in an ATTRv-PN population. While inotersen, another antisense oligonucleotide (ASO) in the same class, is approved with a REMS to mitigate the risks of thrombocytopenia and glomerulonephritis, thrombocytopenia and glomerulonephritis do not appear to be substantial risks with the use of eplontersen. The risk of vitamin A deficiency will be communicated in Section 5 of the labeling: Warning and Precautions.

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), Wainua (eplontersen), is necessary to ensure the benefits outweigh its risks. Ionis Pharmaceuticals, Inc submitted a New Drug Application (NDA) 217388 for eplontersen with the proposed indication of the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv) in adults.[1,2] This application is under review in the Division of Neurology 1. The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Eplontersen, a new molecular entity, is an antisense oligonucleotide (ASO) GalNAc conjugate that causes hepatic-targeted degradation of TTR mRNA (for mutant variants and wild-type TTR) through direct binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.[2] Eplontersen is also known as an ASO inhibitor of human TTR protein synthesis which is proposed for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv) in adults. The proposed dosing regimen for the polyneuropathy indication is 45 mg eplontersen (free acid equivalent) administered subcutaneously with an autoinjector once monthly (every 4 weeks in clinical trials). Eplontersen is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217388 relevant to this review:

- 01/06/2022: Orphan Drug status was granted for eplontersen by the Agency.
- 12/22/2022: NDA 217388 eplontersen submission for the treatment of the polyneuropathy of hereditary transthyretinmediated amyloidosis (ATTRv) in adults received.
- 09/21/2023: A late-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 current safety risks that would require a REMS for eplontersen.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hereditary transthyretin-mediated amyloidosis (ATTRv) is a rare disease that is debilitating, irreversible, rapidly progressive, and fatal. This autosomal dominant disorder is caused by mutations in the gene that codes for transthyretin (TTR) protein. Transthyretin (TTR) is a human 56 kDa non-glycosylated amyloidogenic protein. Autonomic neuropathy (AN) occurs in ~75% of patients with ATTRv, characterised by orthostatic hypotension, gastrointestinal and genitourinary symptoms. Sensorimotor neuropathy which ultimately leads to a loss of ambulatory function, and severe autonomic neuropathy impacts the cardiovascular, gastrointestinal, and genitourinary systems. These effects ultimately lead to declines in quality of life. Patients typically have a life expectancy of 5 to 15 years after diagnosis and typically die due to malnutrition and cachexia, renal failure, and cardiac disease.[2,3]

3.2. Description of Current Treatment Options

The available treatment of ATTRv is focused upon the reduction of the production and subsequent deposit of the pathogenic transthyretin (TTR) protein in target tissue. The following therapies aim to (1) target TTR production, (2) stabilize TTR tetramers and (3) degrade TTR amyloid deposits.[3]

Three FDA-approved therapies are available for the treatment of hATTR (See Appendix 10.1). Patisiran is a transthyretindirected siRNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretinmediated amyloidosis in adults. Patisiran is administered by IV infusion every 3 weeks. It carries warnings and precautions of infusion-related reactions and reduced serum vitamin A levels. Inotersen is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Vutrisiran is a chemically modified siRNA related to patisiran and has prolonged liver residence time, and less frequent dosing (every 3 months) compared to the dosing every 3 weeks for patisiran. Similar to the label for patisiran, vutrisiran is approved with a warning and precaution in labeling to provide vitamin A supplementation to mitigate reduced vitamin A levels. Inotersen is administered weekly by subcutaneous injection. Because of the risks of thrombocytopenia and glomerulonephritis, Tegsedi (inotersen) was approved with a REMS. The Tegsedi REMS requires prescribers and pharmacies be certified and patients are

enrolled in the REMS. To mitigate the risks of serious bleeding with severe thrombocytopenia and glomerulonephritis prescribers must submit documentation that patients are monitored for severe thrombocytopenia, serious bleeding with severe thrombocytopenia, and glomerulonephritis.

While treatment options are available for patients with hATTR amyloidosis with polyneuropathy, additional options are needed for treatments that are effective and safe, have convenient dosing, and do not require intensive laboratory or clinical monitoring.

4. Benefit Assessment

The Phase 3 pivotal trial, ION-682884-CS3, an ongoing, multinational, external placebo-controlled, open-label 84-week study was the single study submitted by the Applicant to demonstrate the effectiveness of eplontersen for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv). The placebo group from the approved inotersen NDA 211172 phase 3 NEURO-TTR study, which enrolled a similar subject population and incorporated similar endpoints to NEURO-TTR, was used as an external control group for the efficacy analyses of eplontersen. There were 144 subjects initially randomized to the eplontersen arm, 24 to the concurrent inotersen arm (the concurrent inotersen reference group was also included in ION-682884-CS3), and 60 to the external control placebo group. Eplontersen 45 mg was given every 4 weeks to determine if it is superior to an external placebo group from the inotersen pivotal study, ISIS 420915-CS2. This inotersen/eplontersen treatment group received inotersen from Weeks 1 to 35. The primary efficacy objective is to study the efficacy of eplontersen at week 35 as compared with the external control of the placebo cohort in the ISIS 420915-CS2 study (NEURO-TTR), evaluating change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7). Changes from baseline in serum TTR concentration in subjects with hATTR-PN were included as a co-primary efficacy endpoint. The secondary efficacy objectives were to evaluate the change from baseline in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN). The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN that was used in the trial has a range from -4 to 136 points, with higher scores representing greater impairment. An interim analysis was conducted at week 35.

The mNIS+7 scores are an objective evaluation of a range of signs and symptoms related to polyneuropathy and a decrease in score indicates improvement. The primary analysis of mNIS+7 included 199 patients: 140 from drug arm and 59 from placebo arm. Results from the clinical trial indicate that there was a statistically significant greater mean reduction in the change in the mNIS+7 from baseline to week 35 compared with placebo. Statistically significant improvements in serum TTR and the Norfolk QoL-DN total score, compared to the external placebo control ($p<0.001$), were also seen at Week 35.

The clinical reviewer concludes that the results of ION-682884-CS3 of eplontersen in adults with hATTR-PN provide clinically meaningful, and statistically significant evidence that eplontersen is effective for the treatment of polyneuropathy in hATTR while the safety profile of eplontersen is acceptable to support an approval without a REMS.[4]

5. Risk Assessment & Safe-Use Conditions

Data from the pivotal study ION-682884-CS3 and the open-label extension study ION-682884-CS13 formed the basis of the clinical safety evaluation. Potential safety concerns for eplontersen based on the route of administration and therapeutic class (including information from the previously approved hATTR drug, inotersen) were thrombocytopenia, glomerulonephritis, renal impairment, abnormal liver function, injection site reactions, flu-like symptoms, central nervous system disorders, hemorrhages, cardiac disorders, and coagulation abnormalities. Potential safety concerns based on the mechanism of action of eplontersen included vitamin A deficiency.

Overall, there were four deaths total, (2.4% of 167 subjects exposed to eplontersen) and were deemed unlikely caused by the investigational drug. There were two cardiac deaths (one each in ION-682884-CS3 and its open label extension study ION-682884-CS13), both in subjects with a history of hATTR-related cardiomyopathy. This section further focuses on the 2 key safety review issues identified by the clinical team including vitamin A deficiency, and thrombocytopenia and glomerulonephritis.[2,9]

5.1. Vitamin A Deficiency

TTR (transthyretin) is a transport protein and one of its major functions is to transport retinol (vitamin A). Since eplontersen's mechanism of action includes the reduction in serum TTR levels, eplontersen has the potential to reduce serum vitamin A levels during treatment. Serum reduction in vitamin A levels have also been seen in other approved medications targeting TTR. Clinical trial protocol required all subjects enrolled in ION-682884-CS3 and -CS13 trials to receive vitamin A supplementation of the daily-recommended dose. Ophthalmology examinations were performed at baseline and at Week 35 in ION-682884-CS3.

The results show that the eplontersen group's mean serum vitamin A levels gradually decreased over time in and remained lower than baseline. Ninety percent of subjects on eplontersen had at least one post baseline vitamin A level that was <LLN (lower limit of normal) despite vitamin A supplementation. A mean serum vitamin A reduction of 71% was seen by Week 37 in ION-682884-CS3. The external placebo group's vitamin A levels remained stable.

An evaluation of ocular TEAEs potentially related to vitamin A deficiency was conducted. No ocular TEAE led to eplontersen discontinuation and there were no TEAEs of night blindness. There were also 8 (5.6%) reports of cataracts in the eplontersen group, compared to 1 (1.7%) in the external placebo group and 0 in the inotersen active comparator group. All subjects had other risk factors for cataracts such as age (ages 60-80), prior cataract history or steroid use. There was one subject with a TEAE of conjunctival hemorrhage that was noted as mild with a baseline ophthalmology exam revealing mild conjunctival congestion. There was one TEAE of xerophthalmia. There were no further cases of vision blurred reported in the 120-day safety update.

The clinical reviewer concludes that there does not appear to be a significant risk of symptomatic vitamin A deficiency in relation to serum vitamin A reduction (and no serious symptoms such as night blindness have been noted). However, it is noted that 95.8% of subjects taking eplontersen in ION-

682884-CS3 had at least one vitamin A reading <LLN despite daily vitamin A supplementation. The risks of Vitamin A deficiency will be communicated in Section 5 of the labeling.

5.2. Thrombocytopenia and Glomerulonephritis

Inotersen, an approved product is also an antisense oligonucleotide (ASO) with the same sequence as eplontersen. Because thrombocytopenia and glomerulonephritis were observed during inotersen clinical trials, the risks are included in boxed warnings for inotersen and inotersen is subject to a REMS to mitigate the risks of thrombocytopenia and glomerulonephritis. Because the risks thrombocytopenia and glomerulonephritis were observed with inotersen these risks were considered AEs of special interest for eplontersen during the review of this application.

The Phase 1 studies did not suggest a relationship between eplontersen and thrombocytopenia or glomerulonephritis, although these studies included a small number of subjects administered few study drug doses. During the Phase 3 pivotal study, ION-682884-CS3 and extension CS13 study, 3 eplontersen subjects (2.1%, 3/144) experienced 4 TEAEs coded as either thrombocytopenia or platelet decreased compared to 1.7% (1/60) in the historic placebo group, 25% (6/24) in the concurrent inotersen group, and 24.1% (27/112) in the historic inotersen group. Two events were coded as "Thrombocytopenia" in 1 eplontersen subject and 2 events as "Platelet count decreased" in 2 eplontersen subjects. None of the thrombocytopenia AEs were serious or led to study drug discontinuation.

Through the 120-day safety update, no eplontersen-treated patients had AEs of glomerulonephritis or nephrotic syndrome. The historical comparator data included 2 placebo patients and 3 inotersen patients that had TEAEs of glomerulonephritis.[9]

Based on the review of the available safety data, the clinical reviewer concludes that thrombocytopenia or glomerulonephritis do not appear to be substantial risks with the use of eplontersen.

6. Expected Postmarket Use

Eplontersen's indication is the same as the already available product in its class, inotersen. The majority of the potential prescribers would be expected to be neurologists. In addition, since eplontersen's molecular design was updated to include a GalNAc conjugation and mixed backbone, its administration is with less frequent dosing intervals compared to inotersen. In addition, because the product's planned availability includes an autoinjector, eplontersen is able to be administered by patients and caregivers in an outpatient, home setting.[2]

7. Risk Management Activities Proposed by the Applicant

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

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of eplontersen on the basis of the efficacy and safety information currently available.[9] The risk associated with eplontersen use is the potential for vitamin A deficiency due to the product's known mechanism of action. This risk will be communicated as a warning in the *Warnings and Precautions* section for "Reduced Serum Vitamin A Levels and Recommended Supplementation." The prescribing information additionally recommends vitamin A supplementation at the recommended daily allowance for patients taking eplontersen.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile of eplontersen is favorable. DRM and DN1 are in agreement that a REMS is not necessary for eplontersen to ensure its 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. FDA-approved Therapies for the Treatment of hATTR

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Dosing/ Administration**	**Important Safety and Tolerability Issues**	**Risk Management Approaches/Boxed Warning, Medication Guide**
FDA-Approved Treatments				
TTR TETRAMER STABILISERS				
Tafamidis (2019)[5]	Treatment of the cardiomyopathy of wild type and hATTR amyloidosis.	61 mg capsule once daily.	No Warnings and Precautions or Contraindications.	Approved with labeling and Patient Information.

Gene Therapies				
Antisense oligonucleotides				
Inotersen (2018)[6]	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.	Injection: 284 mg/ 1.5 mL in a single-dose prefilled syringe, 284 mg administered by subcutaneous injection once weekly.	Serious bleeding caused by severe thrombocytopenia glomerulonephritis.	Approved with labeling, Patient counseling Information, Med Guide, IFU, and a REMS (Tegsedi REMS).
Small interfering RNAs				
Patisiran (2018)[7]	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.	Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial, for patients <100 kg, the recommended dosage is 0.3 mg/kg every 3 weeks by intravenous infusion. For patients ≥100 kg, the recommended dosage is 30 mg	Infusion-related reactions and reduced serum vitamin A levels and recommended supplementation.	Approved with labeling and Patient counseling information.
Vutrisiran (2022)[8]	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.	Injection: 25 mg/0.5 mL in a single-dose prefilled syringe, 25 mg administered by subcutaneous injection once every 3 months.	Reduced serum vitamin A levels and recommended supplementation.	Approved with labeling and Patient counseling information.

10.2. References

1. Ionis Pharmaceuticals, Inc. Proposed Eplontersen Prescribing Information. November 2022

2. Ionis Pharmaceuticals, Inc. Summary of Clinical Safety. November 2022

3. Carroll A, Dyck PJ, de Carvalho M, et al. *J Neurol Neurosurg Psychiatry* 2022;93:668–678.

4. Food and Drug Administration. Division of Neurology 1 (DN1). Wainua (eplontersen). NDA 217388. DRAFT Integrated Review. November 3, 2023.

5. Pfizer Inc. VYNDAQEL (tafamidis meglumine) and VYNDAMAX (tafamidis) Prescribing Information. October 2023.

6. Akcea Therapeutics, Inc. TEGSEDI (inotersen) Injection Prescribing Information. June 2022.

7. Alnylam Pharmaceuticals, Inc. ONPATTRO (patisiran) Lipid Complex Injection Prescribing Information. January 2023.

8. Alnylam Pharmaceuticals, Inc. AMVUTTRA (vutrisiran) Injection Prescribing Information. February 2023.

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