CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215515Orig1s000

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	215515
PDUFA Goal Date	July 14, 2022
OSE RCM #	2021-793
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 13, 2022
Subject	Evaluation of Need for a REMS
Established Name	Vutrisiran
Trade Name	Amvuttra
Name of Applicant	Alnylam Pharmaceuticals, Inc.
Therapeutic Class	Small interfering ribonucleic acid (siRNA)
Formulation	50 mg/mL solution
Dosing Regimen	25 mg administered by subcutaneous injection once every 3 months

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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 Amvuttra (vutrisiran) is necessary to ensure the benefits outweigh its risks. Alnylam Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 215515 for vutrisiran with the proposed indication for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults. The risk associated with the use of vutrisiran is decreased vitamin A, which may contribute to ocular changes (e.g., night blindness). Labeling will include that patients should receive Vitamin A supplements at the recommended daily allowance. The likely prescribers will be neurologists.

The applicant did not submit a proposed REMS or risk management plan with this application. DRM has determined that a REMS is not necessary to ensure the benefits of vutrisiran outweigh the risks of ocular toxicity associated with a decline in Vitamin A levels. This risk will be communicated in the Warnings and Precautions section of the labeling. Vutrisiran offers an additional treatment option for hATTR-PN, a rare serious disease with significant morbidity and mortality.

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) Amvuttra (vutrisiran) is necessary to ensure the benefits outweigh its risks. Alnylam Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 215515 for vutrisiran with the proposed indication for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults. 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

Amvuttra (vutrisiran), a new molecular entity (NME)[a], is a chemically modified double-stranded small interfering ribonucleic acid (siRNA), proposed for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Vutrisiran targets variant and wild-type transthyretin (TTR) messenger RNA (mRNA) and is covalently linked to a ligand containing three N- acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes. It is related to patisiran[1], an siRNA approved for the same indication in 2018, but vutrisiran has been chemically modified for greater metabolic stability, prolonged liver residence time, and less frequent dosing (every 3 months) compared to the dosing every 3 weeks for patisiran.

Vutrisiran is proposed to be supplied as a pre-filled syringe of 25 mg of vutrisiran, to be administered by

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

subcutaneous injection every three months by a healthcare professional for long-term therapy.[b] On May 25, 2018, vutrisiran was granted an Orphan Drug designation and received a Fast-Track designation on April 3, 2020. Vutrisiran is not approved in any other jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215515 relevant to this review:

- 5/25/2018: Orphan Drug designation granted
- 4/3/2020: Fast Track designation granted
- 4/14/2021: NDA 215515 submission for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults received

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Amyloidosis is the general term used to refer to extracellular deposition of subunits of a variety of proteins. These deposits may result in a wide range of clinical manifestations depending on their type, location, and amount of deposition.[2] Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rare, life-threatening, autosomal dominant disorder caused by mutations in the TTR gene that results in rapidly progressive, debilitating morbidity and high mortality.[c] TTR protein, also known as prealbumin, is produced primarily in the liver and is normally a carrier of vitamin A. Mutations in TTR cause abnormal amyloid proteins to accumulate and damage body organs and tissue, most commonly the peripheral nerves and heart, resulting in peripheral neuropathy, autonomic neuropathy, and/or cardiomyopathy.

The clinical presentation of cardiomyopathy most commonly manifests as heart failure, characterized by dyspnea and edema. Angina and claudication can be present, along with syncope related to arrhythmia or heart block, due to the accumulation of amyloid proteins in the coronary arteries. Peripheral neuropathy symptoms include painful dysesthesias in the feet and hands, as well as loss of sensation, which could potentially lead to thermal burns involving the feet and hands and to joint injury in the lower limbs. Progressive muscle atrophy and motor weakness leads to impaired ambulation and inability to perform other activities of daily living. Autonomic neuropathy leads to debilitating orthostatic hypotension, severe gastrointestinal symptoms (including early satiety, chronic nausea/vomiting, and both diarrhea and constipation), and bladder dysfunction with recurrent urinary tract infections. Death usually occurs within 5-12 years after onset, most often due to cardiac

[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.*

dysfunction, infection, or cachexia. The exact incidence of hATTR amyloidosis is unknown and varies geographically, but is estimated to be 1/100,000 in U.S. Caucasians, with a male predominance (approximately 3:1 male to female ratio) with diagnosis typically occurring in the seventh decade.[3,4,d] Approximately 100 to 2500 individuals are estimated to have hATTR-PN in the United States.[5]

3.2. Description of Current Treatment Options

Two FDA-approved therapies are available for the treatment of hATTR. Patisiran is a transthyretin-directed siRNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated 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. Inotersen is administered by weekly subcutaneous injection. Because of the risks of thrombocytopenia and glomerulonephritis, Tegsedi (inotersen) was approved with a REMS. The Tegsedi REMS, is a restricted distribution program that 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.

Other treatment options for hATTR include liver transplant, tafamidis (approved in the U.S. in 2019 for treatment of the heart disease (cardiomyopathy) caused by transthyretin mediated amyloidosis (ATTR-CM) in adults), and diflunisal (off-label use). While treatment options are available for patients with hATTR amyloidosis with polyneuropathy, there remains an unmet medical need for treatments that are effective and safe, have convenient dosing, and do not require intensive laboratory or clinical monitoring.

4. Benefit Assessment

The efficacy and safety of vutrisiran is being studied in an ongoing Phase 3, randomized, open-label, active comparator, and externally controlled study in adult patients (n=122 vutrisiran, n=42 Patisiran, n=77 external placebo control) with hATTR amyloidosis with polyneuropathy known as Helios-A (ALN-TTRSC02-002; NCT03759379).[6] The study is being conducted in 2 parts: an 18-month Treatment Period, with the primary efficacy analysis at month 9 (which are being reviewed for the purpose of this NDA), efficacy analysis at month 18, and followed by an 18-month treatment extension period, in which patients initially treated with patisiran are switched to vutrisiran. Given the life-threatening nature of hATTR amyloidosis and the existence of approved therapies, it would not be ethical to use a concurrent placebo control group in the Helios-A study. The placebo group of the APOLLO study (the pivotal Phase 3

[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.*

study from the approved patisiran NDA 210922; NCT01960348) is used as an external control for the efficacy analyses of vutrisiran. This external placebo group consists of patients with hATTR-PN who are comparable to the hATTR-PN patients enrolled in the Helios-A study. The Helios-A study also includes an active control group receiving the approved treatment patisiran.

The change from baseline to Month 9 on the Modified Neurological Impairment Score +7 (mNIS+7)[e], an objective evaluation of a range of signs and symptoms related to polyneuropathy, is the primary endpoint used for the Helios-A study.[7] The clinical reviewer for vutrisiran concludes that while the mNIS+7 is an acceptable endpoint, the results should be considered in the context of the results of the secondary endpoints, particularly the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score, a patient-reported assessment of the impact of their polyneuropathy.[8]

With regards to the primary endpoint, the month 9 results demonstrated vutrisiran patients experienced an average treatment-effect of 17 points (baseline ~60; 304-point scale) on the mNIS+7 compared to placebo ($p<0.0001$). For the secondary endpoint, there was an average treatment-effect at month 9 of 16 points (baseline ~47; 141-point scale) on Norfolk QOL-DN score for patients in the vutrisiran group compared to placebo ($p<0.0001$).

The clinical reviewer concluded that these results provide substantial evidence of effectiveness based on a reduction of neurological impairment that is inconsistent with the natural history of hATTR neuropathy.[f]

5. Risk Assessment & Safe-Use Conditions

The safety database for vutrisiran includes all patients (n=122) from the Phase 3 externally controlled Helios-A study.[9] The most commonly observed (≥ 5% and at least 2% more frequently in the vutrisiran group than in the placebo group) adverse events associated with the use of vutrisiran were arthralgia, abdominal pain, decreased vitamin A, and dyspnea.

5.1. Reduced Vitamin A levels

A decrease in vitamin A levels is an expected adverse event given vutrisiran's mechanism of action. Because of the demonstrated reduction of vitamin A levels in patisiran (which has a similar mechanism of action), all study patients received the recommended daily amount of vitamin A as a supplement during the Helios-A study. Over the course of the study, median percent reduction in vitamin A levels through Month 9 was 60.9% in the vutrisiran group and 62.6% in the patisiran group. Abnormal visual

[e] The mNIS+7 comprises assessments on polyneuropathy signs (24 items on weakness, five on muscle stretch reflex decrease, and eight on sensation loss; all items are assessed bilaterally) and seven neurophysiologic tests (five attributes of nerve conduction, Smart Somatotopic Quantitative Sensation Testing of touch pressure and heat pain, and heart rate during to deep breathing).

[f] 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.*

adaptation to darkness (night blindness) is a symptom of vitamin A deficiency. Night blindness was reported in 1 (0.8%) subject in the vutrisiran group and in 1 (1.3%) subject in the external placebo group. The clinical reviewer for vutrisiran concluded that labeling for vutrisiran should include a warning and precaution to describe the need for vitamin A supplementation to avoid possible vitamin A deficiency.[10]

5.2. Deaths

Six deaths occurred in the Helios-A study, three in vutrisiran patients and three in patisiran patients. The causes of death in the vutrisiran patients were related to 1) Covid-19 with cardiac amyloidosis, heart failure, and pneumonia; 2) cardiac amyloidosis, cardiac failure, and iliac artery occlusion; and 3) sudden cardiac death (in a patient with a history of cardiac amyloidosis and congestive heart failure), respectively. Mortality was numerically lower in the vutrisiran group (2.5%) than in the external placebo group (8%) or concurrent comparator patisiran group (7%). However, the Phase 3 clinical study was not designed to statistically evaluate an effect on survival and no conclusion regarding a potential long-term survival effect can be made. The clinical reviewer's conclusion is that death rates with vutrisiran are similar to rates that have been reported in the literature for hATTR amyloidosis and it appears unlikely that these deaths were caused by the investigational drug.[g]

6. Expected Postmarket Use

The likely prescribers for vutrisiran will be neurologists. Vutrisiran will likely be administered by a healthcare provider within an office or other healthcare setting.

7. Risk Management Activities Proposed by the Applicant

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

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of vutrisiran on the basis of the efficacy and safety information currently available. Vutrisiran is a chemically modified siRNA related to the currently approved h-ATTR therapy Patisiran. hATTR-PN is a rare serious disease with significant morbidity and mortality, for which vutrisiran offers an additional treatment option. The current treatment options approved for hATTR-PN (patisiran and inotersen) require more frequent dosing (every 3 weeks for Patisiran and weekly for inotersen). Additionally, Inotersen is available only through the Tegsedi REMS due to the risks of thrombocytopenia and glomerulonephritis.

The analysis of the safety data for vutrisiran indicated that there are no serious safety concerns that warrant a REMS. Based on its mechanism of action, vutrisiran is expected to reduce vitamin A levels in

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

the body similar to patisiran. Like patisiran, the label for vutrisiran will include a warning and precaution to provide vitamin A supplementation to mitigate reduced vitamin A levels. While deaths occurred during the study, they were determined to be unrelated to the study drug. Additionally, mortality is high in h-ATTR patients, with death usually occurring within 5-12 years after onset. Based on the currently available data, DRM and DN1 concur that a REMS is not necessary to ensure the benefits of vutrisiran outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for vutrisiran 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 Neurology Products. Approval Letter for NDA 210922 (patisiran), August 10, 2018.

[2] Kyle RA. Amyloidosis: a convoluted story. Br J Haematol 2001; 114:529.

[3] Swiecicki PL, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid. 2015;22(2):123-31.

[4] Plante-Bordeneuve V, Said G. Familial amyloid polyneuropathy. Lancet Neurol. 2011;10(12):1086-97.

[5] Ando Y, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J of Rare Dis. 2013;8(31).

[6] Alnylam. Summary of Clinical Efficacy for Amvuttra, April 14, 2021.

[7] Dyck PJB, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: From NIS to mNIS + 7. J Neurol Sci. 2019 Oct 15;405:116424.

[8] Raine, R. Division of Neurology 1. DRAFT Clinical Review for NDA 215515 Amvuttra (vutrisiran), January 24, 2022.

[9] Alnylam. Summary of Clinical Safety for Amvuttra, April 14, 2021.

[10] Division of Neurology 1. Draft Prescribing Information for NDA 215515 Amvuttra (vutrisiran), February 1, 2022.

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