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Evaluation of Need for a REMS
Patisiran
Onpattro
Alnylam Pharmaceuticals
Small interfering ribonucleic acid (siRNA)
2 mg/ml patisiran and lipid excipients in isotonic phosphate buffered saline
0.3 mg/kg administered intravenously every 3 weeks
# Table of Contents

EXECUTIVE SUMMARY ............................................................................................................. 3

1 Introduction ........................................................................................................................................ 3

2 Background ......................................................................................................................................... 3

2.1 Product Information ......................................................................................................................... 3

2.2 Regulatory History ............................................................................................................................ 4

3 Therapeutic Context and Treatment Options .................................................................................. 4

3.1 Description of the Medical Condition .............................................................................................. 4

3.2 Description of Current Treatment Options ...................................................................................... 5

4 Benefit Assessment ............................................................................................................................ 6

5 Risk Assessment & Safe-Use Conditions ....................................................................................... 7

5.1 Adverse Events of Special Interest .................................................................................................. 7

5.1.1 Deaths ....................................................................................................................................... 8

5.1.2 Infusion Related Reactions ......................................................................................................... 8

6 Expected Postmarket Use .................................................................................................................. 8

7 Risk Management Activities Proposed by the Applicant ............................................................... 9

8 Discussion of Need for a REMS ........................................................................................................ 9

9 Conclusion & Recommendations ..................................................................................................... 9

10 Appendices ....................................................................................................................................... 10

10.1 References .................................................................................................................................... 10

Reference ID: 4284230
EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Onpattro (patisiran) is necessary to ensure the benefits outweigh its risks. Alnylam Pharmaceuticals Inc. (Alnylam) submitted a New Drug Application (NDA 210922) for patisiran with the proposed indication for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). The risk associated with patisiran is infusion related reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Neurology Products (DNP) agree that a REMS is not needed to ensure the benefits of patisiran outweigh its risks. Patisiran showed significant evidence of clinical efficacy for the treatment of adults with hATTR amyloidosis. The risk of infusion related reactions was mild to moderate in severity throughout the course of the clinical development program. Providers who will prescribe and administer patisiran are trained on the signs and symptoms, as well as appropriate management, of infusion related reactions. The Applicant has proposed mitigating this risk via labeling, including a recommendation for premedication prior to each infusion.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Onpattro (patisiran) is necessary to ensure the benefits outweigh its risks. Alnylam submitted a New Drug Application (NDA 210922) for patisiran with the proposed indication for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). This application is under review in the Division of Neurology Products. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Onpattro (patisiran), a new molecular entity (NME)\(^a\), is a double-stranded small interfering ribonucleic acid (siRNA), proposed for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). Patisiran is proposed to be administered as a 2 mg/ml lipid nanoparticle intravenous solution at a dose of 0.3 mg/kg infused over 80 minutes every 3 weeks, for chronic use.\(^b\).

Patisiran targets a sequence in the untranslated region of wild-type (wt) and mutant transthyretin (TTR) mRNA. The lipid nanoparticle formulation facilitates delivery of the siRNA to the liver, which is the primary source of TTR protein in circulation. When administered via intravenous infusion, patisiran is delivered to hepatocytes where it works through the mechanism of RNA interference (RNAi), a biological process by which an siRNA can direct sequence-specific degradation of mRNA, leading to the reduction of the synthesis of the corresponding protein. Patisiran thus inhibits the synthesis of wt and mutant TTR proteins.

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

\(^b\) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
mutant TTR mRNA in hepatocytes resulting in a reduction in circulating TTR protein. Theoretically, a reduction in serum TTR will lead to a decrease in disease-causing amyloid deposits in tissues, thereby impacting polyneuropathy and cardiomyopathy that are the cardinal manifestations of hereditary TTR-mediated amyloidosis (hATTR amyloidosis). Patisiran was designated orphan drug and breakthrough therapy status by the Agency on June 14, 2012, and November 12, 2017, respectively. Patisiran is not currently approved or marketed in any jurisdiction.

2.2 **REGULATORY HISTORY**
The following is a summary of the regulatory history for NDA 210922 relevant to this review:

- 6/14/2012: Patisiran was granted orphan drug designation for the treatment of Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP).
- 10/31/2013: Fast track designation was granted by the Agency for the treatment of TTR-FAP.
- 11/15/2017: Part 1 of 2 of a rolling submission for NDA 210922 was received for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).
- 11/17/2017: Breakthrough Therapy designation was granted to patisiran for the treatment of adults with hATTR amyloidosis.
- 12/7/2017: The Agency granted a request to update the indication for orphan drug designation from the treatment of TTR-FAP to the treatment of hATTR amyloidosis.
- 12/11/2017: Part 2 of 2 of a rolling submission for NDA 210922 was received.
- 2/1/2018: Priority review was granted for NDA 210922.

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.¹ Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rare, life-threatening, autosomal dominant multi-systemic disease caused by mutations in the TTR gene that results in rapidly progressive, debilitating morbidity and high mortality. ² 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

¹ 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.
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.

hATTR amyloidosis has a male predominance (approximately 3:1 male to female ratio) with diagnosis typically occurring in the seventh decade. Median survival is 4.7 years following diagnosis, and is reduced to 3.4 years when cardiomyopathy is involved. Worldwide, it is estimated that 50,000 individuals are affected by hATTR amyloidosis annually.

3.2 **DESCRIPTION OF CURRENT TREATMENT OPTIONS**

There are currently no FDA-approved treatment options for hATTR amyloidosis. The limited treatment available for a small subset of patients includes orthotopic liver transplant (OLT) and TTR tetramer stabilizers. OLT essentially eliminates mutant TTR from the circulation but does not affect the hepatic production of wt TTR, which continues to be made by the transplanted liver. OLT is only effective in slowing the progression of disease in patients with an early age of onset (<50 years of age). Consequently, almost two-thirds of patients with hATTR amyloidosis are not transplant-eligible. Even when OLT is possible, morbidity and mortality are substantial; patients require life-long immunosuppressive medications, with their attendant risks of infection and renal injury.

Tafamidis, a TTR tetramer stabilizer, is approved in Europe, Japan, and certain countries in Latin America, for the treatment of transthyretin amyloidosis in adult patients with stage I symptomatic polyneuropathy to delay peripheral neurologic impairment. It acts by binding to TTR to reduce its misfolding into an amyloid protein. Diflunisal, a generic, oral nonsteroidal anti-inflammatory drug (NSAID), has been used off-label for reports of TTR tetramer stabilization and is used in hATTR amyloidosis patients with both early and late stage neuropathy. Palliative/symptomatic therapies directed at specific symptoms such as pain, nausea, vomiting, and diarrhea have been the mainstay of treatment despite their limited effectiveness. Most patients continue to experience significant morbidity and mortality associated with disease progression due to the unmet medical need for effective therapies.

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\[ \text{d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.} \]
4 Benefit Assessment

Efficacy data for patisiran was collected in 1 pivotal phase 3, randomized, double-blind, placebo controlled study, Study 004 (National Clinical Trial [NCT] 01960348), and supported by data from one open label study, Study 006 [NCT02510261]). Safety was further supported by Study 003 (NCT 01961921), a Phase 2 open-label extension study designed to evaluate the safety of long-term dosing with patisiran.

Study 004 enrolled 225 patients (148 on patisiran, 77 on placebo) for an 18-month treatment period, all of whom had a clinical diagnosis of hATTR amyloidosis, with varying degrees of disease-related neuropathy (mild to severe). Prior therapy with TTR tetramer stabilizers was permitted, but was required to be stopped before the start of study drug to avoid any confounding effects on results. Because patients who have undergone OLT no longer produce mutant TTR and are at risk for developing liver function test (LFT) abnormalities due to graft rejection, these patients (or patients expecting to undergo OLT during the study period) were excluded. Patisiran was administered at a dose of 0.3 mg/kg every 3 weeks, infused over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, increasing to approximately 3 mL/min for the remainder of the infusion. All patients received premedication including corticosteroids, H1 and H2 blockers, and acetaminophen or equivalents, to reduce the risk of infusion related reactions (IRR) that can be seen with IV administered lipid based formulations. The primary endpoint of Study 004 was the difference between patisiran and placebo in the change from baseline to 18 months of the Modified Neurologic Impairment Score +7 (mNIS+7), a disease-specific composite measure of polyneuropathy. Secondary and exploratory endpoints measured the effects on cardiac structure and function, and overall impact on quality of life, motor strength, disability, ambulatory ability, nutritional status, and autonomic symptoms. Study 004 met its primary endpoint, with patisiran patients experiencing a mean change from baseline in the mNIS+7 of -6.03 (improvement in neuropathy), versus a mean change of 27.96 in placebo patients (worsening neuropathy). This accounted for a difference of -33.99 between the two study groups (p<0.001). All secondary endpoints demonstrated statistically significant results as well (all p-values < 0.001).

Study 006 is an ongoing open-label, single-arm, long-term follow-up extension study for patients completing Study 004 or Study 003 (NCT01961921, a phase 2 long-term dosing study). Patients on TTR tetramer stabilizers in Study 003 were permitted to continue those drugs while enrolled. The purpose of Study 006 is to examine the long-term safety and maintenance of efficacy for up to 5 years; mNIS+7 is being evaluated at the end of the first year of treatment (Month 12), after which NIS will be performed annually. Interim data is available with a cutoff date of July 14, 2017, and preliminarily shows a mean reduction in mNIS+7.5
The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on reliable and statistically strong evidence that patisiran can improve the neuropathy and quality of life of these adults.\textsuperscript{5,e}

5 Risk Assessment & Safe-Use Conditions

The safety database supporting this application for marketing approval includes data from 219 patients across 3 studies (Study 004, 006, and 003), and includes 179 patients treated for ≥12 months, 101 patients treated for ≥24 months, and 32 patients treated for ≥36 months. In total, the safety database represents 412.3 patient-years of exposure to patisiran.

AEs that were reported in ≥10% of patisiran patients are presented below:

- Diarrhea (37.2%)
- Fall (16.9%)
- Constipation (14.9%)
- Nausea (14.9%)
- Dizziness (12.8%)
- Urinary Tract Infection (12.8%)
- Fatigue (12.2%)
- Headache (10.8%)
- Cough (10.1%)
- Insomnia (10.1%)
- Nasopharyngitis (10.1%)
- Vomiting (10.1%)

The proportion of patients who had a severe adverse event (SAE) was 28.4% in patisiran and 36.4% in placebo. Peripheral edema was reported in 44 patients (29.7%, 69 events) in the patisiran group and 17 patients (22.1%, 35 events) in the placebo group. The majority of these patients had a medical history of cardiac disorders, which can lead to peripheral edema. The Applicant proposes addressing peripheral edema in labeling, under Section 6 of the Prescribing Information (PI).

Because patisiran targets TTR mRNA and results in reduction of TTR serum levels and associated transport proteins such as retinol binding protein (RBP), which is a carrier of vitamin A in the serum, patients were instructed to take a daily supplement containing the recommended daily allowance of vitamin A during the study; this will continue to be recommended to patients in the labeling.

5.1 Adverse Events of Special Interest

\textsuperscript{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.
5.1.1 Deaths
A total of 20 deaths, 14 in patisiran patients and 6 in placebo patients, have been reported in the 3 studies which comprise the safety database. Overall, patisiran treated patients were enrolled at a ratio of 2:1 when compared to placebo, therefore there was no imbalance in deaths between the two groups. Within the pivotal Phase 3 Study 004, In Study 004, a total of 13 deaths were reported, with 7 deaths (4.7%) in the patisiran group and 6 deaths (7.8%) in the placebo group. The rate of death observed in the patisiran group (3.20 deaths per 100 patient-years) is lower than the rate in the placebo group (6.24 per 100 patient-years) and falls at the lower end of expected numbers in populations of patients with hATTR amyloidosis, which ranges from 3 to 6 deaths per 100 patient-years. All of the deaths were considered unlikely or not related to study treatment by the investigators and most likely related to the underlying disease or other factors. The clinical reviewer concurs with the conclusion that patisiran is not related to deaths in the patisiran treated subjects. Most of the deaths were adjudicated as cardiovascular (CV) in nature, as expected in a hATTR population.

5.1.2 Infusion Related Reactions
IRRs are a known risk of patisiran and other lipid drug formulations. In order to reduce the potential for an IRR, all patients in the patisiran clinical studies (including placebo patients in Study 004) received a premedication regimen consisting of corticosteroids, H1 and H2 blockers, and acetaminophen or equivalents to reduce the potential of an IRR. During the clinical development period, 2 premedication regimens were used: the original regimen and a subsequent reduced regimen. In the original regimen, the premedication was given in the evening 12 hours prior to study drug administration and on the day of study drug administration at least 60 minutes prior to the start of the infusion. In the reduced regimen, the premedication is only given on the day of study drug administration at least 60 minutes prior to the start of the infusion.

IRRs were reported in 18.9% of patisiran patients versus 9.1% of placebo patients. All IRRs were mild to moderate in severity and resolved. There have been no SAEs of anaphylaxis, anaphylactoid, or severe hypersensitivity reactions in the clinical development program. The proposed label for Patisiran will include language in the PI in section 2, Dosage and Administration, indicating that patients should receive an intravenous premedication regimen prior to each infusion, with equivalent oral dosing being an alternative to patients who may not tolerate the intravenous formulations.

6 Expected Postmarket Use
The likely prescribers for patisiran will be neurologists on a multi-disciplinary team based out of regional amyloidosis centers. Patisiran will likely be administered by a healthcare provider within a hospital or infusion center environment, with the potential for home-based infusion for select candidates. These providers are trained on the signs and symptoms, as well as appropriate management, of IRRs. The

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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.
proposed labeling stipulates that a premedication regimen should be used prior to each infusion, to mitigate the risk of IRRs, as is standard with many infused medications.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for patisiran beyond routine pharmacovigilance and labeling. The Applicant proposes that use of the label and compliance with standard safety reporting and pharmacovigilance requirements will suffice to mitigate risks and preserve benefits.

8 Discussion of Need for a REMS

hATTR amyloidosis is a progressive, orphan disease with high morbidity and mortality, with patients surviving on average less than 5 years after diagnosis. There is an unmet medical need in this patient population as the only treatment option at this time is OLT in qualified candidates, and no approved pharmacologic therapies are available.

Based on the results from the pivotal trial, Study 004, patisiran demonstrated efficacy and safety based on significantly improved results in the mNIS+7 versus patients treated with placebo. The clinical reviewer recommends approval of patisiran on the basis of the efficacy and safety information currently available.\(^5\)

No serious safety issues have been identified with patisiran, and the risk of IRRs in the clinical development program were mild to moderate in severity. The proposed labeling includes the risk of IRRs in the Warnings and Precautions (Section 5) and recommends the use of a premedication regimen to reduce the likelihood of IRRs. Patisiran will likely be administered by healthcare providers in infusion centers or other similar healthcare settings. Home administration by a healthcare practitioner may be permitted for certain candidates unable to travel to an infusion center. Whether administered at an infusion center or as a home based-infusion, there is a trained healthcare provider available to monitor for potential IRRs and to treat appropriately if necessary.

DRISK agrees that the adverse event profile of the drug does not warrant risk mitigation beyond labeling. Based on the currently available data, DRISK and DNP concur that a REMS is not necessary to ensure the benefits of patisiran outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for patisiran to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.
Should the Division of Neurology Products have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References


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/s/

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