CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210922Orig1s000

Trade Name:	Onpattro 2 mg/mL injection for intravenous use
Generic or Proper Name:	patisiran
Sponsor:	Alnylam Pharmaceuticals, Inc.
Approval Date:	August 10, 2018
Indication:	For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210922

NDA APPROVAL

Alnylam Pharmaceuticals, Inc.
Attention: Andrew Slugg
Vice President, Regulatory Affairs
300 Third Street
Cambridge, MA 02142

Dear Mr. Slugg:

Please refer to your New Drug Application (NDA) dated December 11, 2017, received December 11, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onpattro (patisiran) lipid complex injection 2mg/mL.

This new drug application provides for the use of Onpattro (patisiran) lipid complex injection for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling [text for the prescribing information (PI)]. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on May 16, 2018, as soon as they are available, but no

more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210922**." Approval of this submission by FDA is not required before the labeling is used.

In addition, we refer to your August 3, 2018, submission in which you commit to implement the carton and immediate container label revisions requested in our August 1, 2018, correspondence. Specifically, you agree to:

- Increase the prominence of the established name on the carton and immediate container label to be commensurate with that of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features.

- Add the following material information from Section 16.2 of the attached, agreed-upon PI, "Do not freeze. **Discard vial if it has been frozen**." (Emphasis added)

The above revisions should be made to the carton and immediate container labels at the time of next printing, but no later than 120 days from the date of this letter. You should submit a "Changes Being Effected" supplemental application to notify us of this change.

PRODUCT QUALITY/EXPIRATION DATING PERIOD

The Agency has assigned an expiration dating period of 24 months for the ONPATTRO (patisiran lipid complex injection) finished product. (b) (4)

ADVISORY COMMITTEE

This application was not referred for review to an advisory committee because the safety profile of patisiran is acceptable for the intended population, the clinical trial design is acceptable, and the efficacy findings were clear.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, or infant outcomes resulting from the use of Onpattro.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3425-1 Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Onpattro (patisiran) during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

The timetable you submitted on June 14, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	09/2019
Study Completion:	10/2030
Final Report Submission:	10/2031

Submit clinical protocol(s) to your IND 117395 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3425-2 Development and validation of a new in vitro drug release method and setting of the drug release acceptance criteria for the finished drug product

The timetable you submitted on May 31, 2018, states that you will conduct this study according to the following schedule:

Submission of the interim PMC Report within 6 months from NDA's action date (as Type B WRO)	2/12/2019
Submission of the final PMC Report within 12 months from NDA's action date (as Prior Approval CMC Supplement to the NDA)	8/12/2019

Submit clinical protocols to your IND 117395 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, the number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

POST-APPROVAL QUALITY AGREEMENTS

We would like to remind you of the following post-approval quality agreements included in the amendment dated April 27, 2018 (SD-20).

- To provide the full-scale commercial manufacturing process data to support the in-process (b) (4) by December 31, 2019.

- To validate the (b) (4) method for the representative ((b) (4)) impurities [(b) (4) for both strands of the patisiran drug substance and to provide the data to FDA by December 31, 2018. Per FDA's '*Guideline for Industry: Text on Validation of Analytical Procedures*,' quantitative test methods for impurities should include validation of specificity, linearity, precision (repeatability), intermediate precision, accuracy, range, and LOD/LOQ.

- To provide the validation data with respect to impurities for the drug product (b) (4) methods post approval by December 31, 2018.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Annie Nguyen, Regulatory Project Manager, by email at Anhtu.Nguyen@fda.hhs.gov or by phone at (240) 402-4460.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELLIS F UNGER
08/10/2018