Patisiran: Product Stability

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for ONPATTRO® (patisiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

INDEX

RELEVANT INFORMATION

Active Substance Stability

Chemical and Physical Stability[1]

The stability of the patisiran active substance was assessed on batches stored for up to 30 – 48 months under long-term conditions (-20°C±5°C) and for up to 6 months under accelerated conditions (25°C/ 60% RH) following the ICH guideline. In addition, one patisiran batch was stored up to 60 months under long-term conditions (-20°C±5°C).

Samples of patisiran active ingredients were tested for appearance, impurities, assay, and water content. Under long term storage conditions, all tested parameters were within the specification limits. Under accelerated conditions, product degradation increased and generated impurity peaks that coincide with thermal degradants (2',5'-isomers, shortened sequences).

In forced degradation studies at stress conditions, patisiran active substance was exposed to extremes of thermal, acidic, basic, oxidative, and photolytic stress. The major degradation products of the patisiran substance included products of depurination, depyrimidation, base cleavage (nucleobases missing from the 3' or 5' end), thymine dimers (only upon extreme photolytic stress), isomers (primarily 2'5' – isomers) or strand cleavage. The major thermal degradants reported during the study were consistent with those obtained in the accelerated storage of the active substance. Under the long-term storage conditions (-20°C±5°C), there was little or no report of the specified degradants.

Based on the available stability data, the active substance was determined to be sufficiently stable.

Photostability[1]

Photostability testing of patisiran active substance was performed following the ICH guideline Q1B with exposure to both cool white fluorescent and near UV light. The results demonstrated that no major photolytic impurities were formed.

Product Stability

Chemical and Physical Stability[1]

The stability of the patisiran finished product was assessed on batches stored for up to 36 months under long-term conditions (2–8°C) and for up to 6 months under accelerated conditions (25°C/ 60% RH) following the ICH guideline.

Samples of the patisiran finished product were tested for appearance, purity of active substance, assay, lipid content, siRNA encapsulation, pH, osmolality, particle size, particulate matter, bacterial endotoxins, sterility, and container integrity. All tested parameters were within the specification limits through 36 months.

In forced degradation studies at stress conditions, patisiran finished product was exposed to thermal, acidic, basic, and oxidative stress. Varying levels of degradation of active substance and lipid components with reduction in duplex purity under all stress conditions.

An in-use study of the chemical and physical stability of the patisiran admixture was conducted. The admixtures were assessed at clinically relevant concentrations representing two-fold differences in patient weight (50 kg and 104 kg) under simulated conditions of use at 30°C±2°C/75%±5% RH, and ambient fluorescent lighting, following simulated infusion using clinically relevant equipment, filters, administration sets, and supplies. The results of the in-use stability assessment confirm the physical and chemical stability of the admixture at clinically relevant concentrations following a 16-hour hold-time in the infusion bag (0.9% NaCl) at a customary room temperature (up to ICH* climatic Zone IVb) and followed by a simulated infusion under ambient lighting.

Based on available stability data, the proposed shelf-life of 24 months when stored at 2-8°C was determined to be acceptable.

Photostability[1]

Photostability testing was performed following the ICH guideline at Q1B with exposure to both cool white fluorescent and near UV light. The results indicated that no special protection from light is required during storage of the patisiran finished product.

Diluted Patisiran Solution Stability

Studies designed to evaluate the stability of the diluted patisiran solution following transport have not been conducted to date.

Patisiran may form small amounts of aggregated particles if stored at room temperature and if subjected to mechanical stress, such as in conditions of shipping, shaking, or vibrations. The dilution of patisiran in saline solution in the infusion bag exposes the patisiran LNP to a diluted, hydrophilic environment that increases the tendency of the LNPs to aggregate. During the time of exposure of patisiran to room temperature, excessive shaking or vibrations may create aggregated particles that can clog the 1.2 µm in-line infusion filter, which may require replacement. Therefore, the infusion of patisiran is recommended to be started as soon as possible after preparation of the admixture with as little disturbance to the infusion bag as possible.[2] Precipitation of the diluted patisiran solution has been observed following road transportation.[3]

CLINICAL DATA

Relevant Clinical Trial Information

The Phase 3 studies (APOLLO and APOLLO-B) and Global OLE study were conducted at multiple sites worldwide. Patisiran doses were prepared and administered under the supervision of the unblinded site personnel at each study site.[4–6]

Home Infusion

In the postmarketing setting, for patients receiving home infusions, doses of patisiran are prepared at the home of the patient by a healthcare professional.[7]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The DOSAGE AND ADMINISTRATION section provides the following information[8]:

ONPATTRO should be administered by a healthcare professional.

ONPATTRO must be filtered and diluted prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- *Remove ONPATTRO from the refrigerator and allow to warm to room temperature. Do not shake or vortex.*
- *Inspect visually for particulate matter and discoloration. Do not use if discoloration or foreign particles are present. ONPATTRO is a white to off-white, opalescent, homogeneous solution. A white to off-white coating may be observed on the inner surface of the vial, typically at the liquid-headspace interface. Product quality is not impacted by presence of the white to off-white coating.*
- *Calculate the required dose of ONPATTRO based on the recommended weight-based dosage.*
- *Withdraw the entire contents of one or more vials into a single sterile syringe.*
- *Filter ONPATTRO through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.*
- *Withdraw the required volume of filtered ONPATTRO from the sterile container using a sterile syringe.*
- *Dilute the required volume of filtered ONPATTRO into an infusion bag containing 0.9% Sodium Chloride Injection, USP for a total volume of 200 mL. Use infusion bags that are di(2-ethylhexyl)phthalate-free (DEHP-free).*
- *Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.*
- *Discard any unused portion of ONPATTRO.*
- *ONPATTRO does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time). Do not freeze.*

The HOW SUPPLIED/STORAGE AND HANDLING section provides the following information[8]:

Storage and Handling

Store at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard vial if it has been frozen.

If refrigeration is not available, ONPATTRO can be stored at room temperature up to 25°C (up to 77°F) for up to 14 days.

For storage conditions of ONPATTRO after dilution in the infusion bag, see Dosage and Administration section.

ABBREVIATIONS

ICH = International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; LNP = lipid nanoparticle; OLE = open-label extension; RH = relative humidity; siRNA = small interfering ribonucleic acid; UV = ultraviolet.

Updated 15 December 2024

REFERENCES

1. Onpattro : EPAR – Public assessment report. European Medicines Agency. Published October 30, 2018. Accessed December 15, 2024. https://www.ema.europa.eu/documents/assessment-report/onpattro-epar-public-assessment-report_.pdf.
2. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-2200063.
3. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-2200064.

4. Protocol for: Adams D, González-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
5. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-1800584.
6. Protocol for: Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
7. Alnylam Pharmaceuticals. Data on file.
8. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.