ONPATTRO® (patisiran)

Product Fact Sheet

- ONPATTRO® (patisiran) lipid complex injection was the first FDA-approved RNAi (RNA interference) therapy for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR-PN) amyloidosis in adults.[1]
- hATTR is a rare, inherited disease characterized by symptoms that affect multiple body systems and is caused by the progressive deposition of toxic misfolded transthyretin (TTR) protein, which accumulates and leads to the manifestation of disease symptoms in multiple sites in the body, including the nerves, heart and digestive system.[2-5]
- ONPATTRO harnesses the body's natural process to silence TTR messenger RNA and reduce the production of TTR protein in the liver, which addresses the underlying cause of hATTR-PN.[1]
- ONPATTRO is administered via intravenous (IV) infusion once every three weeks by a healthcare professional, and the dose is based on actual body weight.[1] Home administration may be an option depending on a patient's insurance and doctor's recommendation.
- The efficacy and safety of ONPATTRO were evaluated in APOLLO, the largest placebo-controlled study evaluating patients with hATTR-PN. In this study, ONPATTRO was shown to significantly improve polyneuropathy at 18 months — with the majority of patients experiencing a reversal in neuropathy impairment from baseline — and improved quality of life, reduced autonomic symptoms and improved activities of daily living at 18 months relative to placebo.[6,i]
- In the study, the most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).[1]
- For more information about ONPATTRO, please visit **ONPATTRO.com**.

Please see Important Safety Information on page 3 and access full Prescribing Information.

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

[i] Reversal defined as mNIS+7 change from baseline of <0 points.[6]

ONPATTRO® (patisiran) Clinical Trial Results at a Glance

- The FDA approval of ONPATTRO was based on positive results from the APOLLO clinical study, a global, randomized, double-blind, multicenter, placebo-controlled Phase 3 study of 225 patients with hATTR-PN.[6]
    - The primary endpoint of the APOLLO study was the change from baseline at 18 months in the modified Neuropathy Impairment Score +7 (mNIS+7), which assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure.[7,ii]
        - Patients treated with ONPATTRO had a mean 6.0-point decrease (improvement) in mNIS+7 from baseline compared to a 28.0-point mean increase (worsening) for patients in the placebo group, resulting in a 34.0-point mean difference relative to placebo, after 18 months of treatment.[6]
        - The majority of ONPATTRO-treated patients (56%) at 18 months of treatment experienced reversal of neuropathy impairment (a decrease from baseline in mNIS+7), compared to four percent of patients who received placebo.[6]
    - The majority of ONPATTRO-treated patients (51%) also experienced an improvement in quality of life at 18 months relative to their own baseline as measured by the Norfolk Quality of Life Diabetic Neuropathy (QOL-DN) Score[iii], compared to 10% of placebo-treated patients.[6]
    - At 18 months, patients treated with ONPATTRO experienced significant benefit compared to placebo for all other secondary efficacy endpoints, including measures of activities of daily living, walking ability, nutritional status and autonomic symptoms.[6]
    - Mean serum TTR levels were reduced by approximately 80% within 10 to 14 days after a single dose, with an 84% mean reduction of serum TTR at 18 months.[1]
    - The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%). To reduce the risk of infusion-related reactions patients received premedications prior to infusion.[6]
    - ONPATTRO also reduced serum vitamin A levels. Patients should take the recommended daily allowance of vitamin A, and tell their physician if they experience symptoms suggestive of vitamin A deficiency (e.g., night blindness).

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[ii] mNIS+7 has a score range from 0-304 points, with higher scores representing a greater severity of disease.[7]

[iii] Norfolk QoL-DN is a patient-reported assessment that evaluated neuropathy in domains such as physical functioning, activities of daily living, symptoms and autonomic neuropathy (total score range from -4 to 136, with higher scores representing greater impairment).[8-10]

IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO® (patisiran). In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRS with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g. night blindness).

Adverse Reactions

The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

For additional information about ONPATTRO, please see the full Prescribing Information.

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About RNAi Therapeutics

- RNAi is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today.[11] This discovery was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine.[12]
- By harnessing the natural biological process of RNAi occurring in our cells, a new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function by silencing messenger RNA (mRNA) – the genetic precursors that encode for disease-causing proteins – thus reducing their production.[11]
- The FDA approval of ONPATTRO® (patisiran) for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults in August 2018 marked the arrival of RNAi therapeutics.

Access to ONPATTRO: Alnylam Assist®

The Alnylam Assist program offers support services to patients throughout their treatment with ONPATTRO, including helping patients understand their insurance coverage and options for financial support based on eligibility. An Alnylam Case Manager will work with a patient to begin treatment with and maintain access to ONPATTRO. An Alnylam Patient Education Liaison can provide education to help patients and their family members better understand the disease and answer questions about ONPATTRO. Learn more about Alnylam Assist by visiting **AlnylamAssist.com/ONPATTRO**.

1 ONPATTRO Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.

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Alnylam® PHARMACEUTICALS

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